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PULMONARY FIBROSIS AND EMPHYSEMA *

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IN the consideration of these chronic pulmonary conditions I propose in the first place to present them not as independent clinical entities but as coexistent conditions mutually dependent upon each other and associated with all chronic lung disease of whatever causation; and secondly, to emphasize the clinical importance of the functional pathological changes associated with these conditions, as distinct from the tissue pathological changes with which their names are usually connected.

DEFINITIONS

We might begin this consideration with our definition of these conditions in terms of function.

Pulmonary fibrosis we would define as an irreversible failure of the self-cleansing power of the lungs.

Emphysema we would define as the irreversible failure of the pulmonary retraction power.

In order to make our meaning clear we may explain that in the case of fibrosis any form of air space obliteration in the lungs (atelectasis, edema, infiltration) is essentially a phenomenon involving both failure of the respiratory and of the self-cleansing functions. Usually the condition is reversible, and then the affected lung areas may reëstablish their function. If, however, the failure becomes permanent, then pulmonary fibrosis is the result, as an expression of the irreversible failure of the self-cleansing power.

In the case of emphysema we have a hyperdistention of certain lung areas, with unequal distribution of the air in the lungs. This condition is at first reversible, as in what we are accustomed to call compensatory emphysema; that is, if the causative factor is removed, the normal retraction power of the affected areas may reassert itself. If, however, the untoward conditions are prolonged, or, as in old age, essential pulmonary tissue changes have occurred, then the retraction power of the lungs cannot be regained;

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that is, the condition becomes irreversible and true emphysema results. How these two conditions, fibrosis and emphysema, interact upon each other, and how the distribution of each in the lungs is affected by the other, will be emphasized and their clinical significance discussed.

The ideas expressed in this paper are due largely to the stimulus gained from the interest in the functional pathology of the lungs which has been developed by Dr. Israel Rappaport of our staff, and we have also been fortunate in obtaining the coöperation of Dr. Dickinson Richards of the Presbyterian Hospital and Dr. André Cournand of our Bellevue staff in the elaboration of the technical details. I am under great obligation to these associates for aid in the preparation of the material here presented.

The Functional Pathogenesis of Pulmonary Fibrosis

The lungs present the most extensive surface of the body that is exposed to the outside air. On account of this exposure as well as the delicacy of their structure, the lungs need special protection to preserve their most important vital function, namely, respiration.

Damaging influences from the outside air are of various sorts. They may be infectious, chemical, or physical in nature, but the damage produced results in each instance in the same tissue response, namely, the replacement of specifically organized tissue by nonspecific connective tissue.

The effects of these influences are frequently most marked in the lower and posterior areas of the lungs, as these regions are more directly exposed through the larger descending bronchi and also because they are the most dependent portions and so less amenable to natural drainage. We consequently are apt to find many forms of pulmonary fibrosis most regularly in the lower lobes.

The pathogenesis of this condition may be considered first as bronchial infection or exudation, with the action of the ciliated epithelium impaired or destroyed, the normal bronchial movements impeded and the air passages occluded. Then follows the clogging of lymphatics through an exudate of large mononuclear cells commonly designated as "dust cells"; and this exudate later becomes organized into fibrous tissue, which begins to form in the walls of the bronchi and gradually extends into the peribronchial tissue, resulting in diminution of efficient respiratory space, impairment of self-cleansing function, and increased susceptibility to subsequent bacterial infections.

Clinical Forms of Fibrosis

There are certain characteristics common to all forms of pulmonary fibrosis of whatever etiology, but for convenience the conditions may be divided into certain clinical categories:

1. *Pre-Clinical Forms.* Under ordinary conditions of modern life, particularly in cities, the lungs of all persons are constantly exposed to

various of the damaging influences already mentioned. Everyone is exposed to frequent repetitions of minor pulmonary infections such as common colds, grippe, bronchitis, etc. In cities and industrial centers the lungs are exposed to constant aspiration of particulate matter, fumes and gases. The cumulative effect of these influences invariably results in a certain degree of pulmonary fibrosis. Some individuals are more predisposed than others because of the nature of their environment, or perhaps particularly because of certain constitutional characteristics, and as age increases, the cumulative effect of these influences of course becomes more pronounced. In the majority of instances the total effect is comparatively slight, the ability of the lungs to continue normal function is great, and the fibrosis that occurs does not present a clinical problem. But nevertheless it must be borne in mind as a basis upon which under more severe or more prolonged injurious influences definite damage occurs, with definite clinical symptoms.

2. *Infectious Fibroses.* These forms of pulmonary fibrosis are those which have involved the parenchyma of the lungs in the manner already described, as the result of more or less well defined clinico-pathologic lung conditions of an infectious nature. Here are included all of the usual chronic lung infections such as pulmonary tuberculosis, interstitial pneumonitis, chronic suppurative conditions, and the like.

3. *Occupational Fibroses.* These are usually included under the general term of pneumonokoniosis,—of which silicosis is the best known example. They are fibrotic processes involving primarily the lymphatics of the lungs which represent the results of considerable or prolonged exposure to industrial dust or other similar agents.

4. *Vascular Fibroses.* This type is really a pulmonary arteriosclerosis and includes the fibrotic processes affecting primarily some part of the vascular system of the lungs. Many of these forms are of unknown etiology, but some of them are well recognized clinical entities, particularly those in which the pulmonary changes are associated with chronic valvular heart disease or with chronic cardiovascular disease, and likewise that interesting clinical condition which we have come to know under the name of Ayerza's disease.

It must be understood that the line of cleavage between the processes included in these four groups is never very sharp. The pre-clinical fibroses gradually go over into the infectious or industrial forms, the infectious forms include many conditions which border on the industrial types, and again in the pneumonokonioses, supervening bronchiectatic or pleuritic processes may add a purely clinical element to the picture, and, finally, more or less vascular sclerosis is characteristic of all other forms of pulmonary fibrosis, although it is only in one distinct group of conditions that this appears to be the chief pathological basis of the disease.

The Functional Pathogenesis of Pulmonary Emphysema

The cause of pulmonary emphysema has been the subject of extensive controversy which is not yet satisfactorily settled. It may therefore be helpful to review briefly some of the various theories which have been advanced to explain the pathogenesis of emphysema, as a basis from which we may lead up to more modern concepts.

It is well known that emphysema develops in old people. It is an invariable accompaniment of the aging process and in this sense may be considered as a physiological change. When however, as is not uncommon, this condition develops in a person under 50 years of age, it may be considered pathological.

The production of pulmonary emphysema has long been ascribed to individual constitutional characteristics, and it has been suggested that these may be hereditary. It has been noted also that such tendencies are accentuated when the work of the individual entails exertion out of proportion to his constitutional capacity.

Again, it has been observed that emphysema may be brought about by prolonged intrapulmonary pressure due to air passage obstruction, as in bronchial asthma or in more chronic obstructing conditions.

Its causation has also been ascribed by Freund [1] to immobilization of the bony thorax associated with calcification of the rib cartilages or of the intervertebral disks, and this view has in the past been widely accepted. It is challenged, however, by Schenker [2] who believes that the chest wall changes are primarily a chronic contraction of the intercostal muscles, leading to fixation of the chest in the expanded position, and that the bony changes are secondary to this. In a similar way, flattening and immobilization of the diaphragm widen the costal arch and lead to fixation of the lung, and this has been looked upon as an accessory cause of emphysema.

Also the fact that the upper accessory muscles of respiration are brought prominently into play and become chronically contracted, has been thought to be an explanation of the tendency of emphysema to localize itself in the upper and anterior portions of the lungs.

The association of emphysema with cases evidencing failure of pulmonary circulation, as in chronic cardiac and cardiovascular disease, has long been recognized and explained on the basis of the increased fixation of the chest cage.

The picture is further complicated by the clinical recognition of what we term compensatory emphysema. When a considerable portion of the lung loses its normal ventilatory function from any cause, then the remaining lung areas take on added activity and the alveoli dilate to compensate for this loss. This condition is frequently confused with true emphysema, but as van Leeuwen and his associates [3] have shown in their studies of asthma and emphysema, compensatory emphysema is a reversible and consequently recoverable condition. Often a return to normal occurs when

the bronchial obstruction or other cause of ventilatory embarrassment is relieved. Emphysema which is at first compensatory and reversible may become permanent and irreversible, but only after a protracted time and comparatively rarely.

There is still another condition, not so generally recognized, although it was originally described by Laennec [4] and has recently again been emphasized by another French clinician, Célice,[5] namely, pulmonary hypertrophy. This is a true regeneration of new lung tissue as a compensatory process, and is neither the temporary passive distention of existing lung areas, compensatory emphysema, nor the permanent loss of lung retraction power, true emphysema. We shall return to the consideration of this most interesting lung condition later in our discussion of intrinsic lung function.

Modern Concepts. It remained for Neergaard [6] to furnish the most modern and most brilliant conception of the pathogenesis of emphysema.

He considers the condition, as we do, as an irreversible loss of retraction power in the lung. This retraction power has always been considered, however, the function of the recoil of the elastic tissue of the lungs.

Neergaard recognizes this function, but considers that it represents only 25 per cent of lung retraction power. The dominating 75 per cent of this power he believes is exerted by the surface tension which develops at the point of contact between the air and the film of moisture which covers the alveolar walls and the capillary air passages. This tension acts in the same direction and in association with the recoil of elastic tissue.

When interruption of communication occurs in a large number of air passages, as, for example, from exudates or bronchial muscle spasm, a compensatory hyperexpansion occurs to open up these communications, and the pulmonary elasticity is increasingly called upon. This overexpansion of alveolar surface of necessity diminishes the surface tension, and the retraction power suffers. As the hyperexpansion continues, the return to the normal becomes increasingly difficult, although the elastic forces of the chest wall are now favoring expiration instead of inspiration, and at best the lung can return from a condition of *volumen pulmonum auctum* to a position of normal inspiration, and this is the state of irreversible emphysema.

Luisada,[7] who has also made valuable contributions to the modern knowledge of emphysema, believes that inflammatory changes in the air spaces lead to degeneration of the smooth muscle tissue in the walls of the bronchioles and alveolar ducts, and he considers that these changes, in conjunction with the factor of diminished surface tension noted by Neergaard, favor the development of the distended air spaces, the thinning or breaking-through of the alveolar walls, and the loss of elasticity and retraction power of the lungs, all of which are characteristic of irreversible emphysema.

Therefore, according to these observers as well as other modern students of the subject, the original cause of emphysema arises in the air spaces and is usually in the nature of an inflammation. The associated changes

in the chest wall, which have been above described as the cause of emphysema, would consequently, according to this hypothesis, be secondary processes resulting from the effort to compensate for the failure of the retraction function of the lung.

So, finally, we find that in emphysema, as in the case of pulmonary fibrosis, we must look for the first evidences in the air spaces themselves. This, as we shall see later in our consideration of the clinical features of these diseases, attaches a very important significance to those early and slight manifestations of pulmonary dysfunction which are often looked upon as cases of simple bronchitis of no serious significance.

Viewed from this angle, the close association which has always been recognized to exist between fibrosis and emphysema and bronchitis, does not necessitate an explanation of the bronchitis as secondary to the fibrosis and emphysema; but rather the so-called bronchitis, when prolonged or often repeated, would be the early manifestation of the more serious failure of lung function which we recognize clinically as fibrosis or emphysema.

The Reciprocal Relationship between Pulmonary Fibrosis and Emphysema

This similarity in their method of pathogenesis is only the beginning of the close connection which exists between these two conditions. They are almost always associated together; when one is found the other also exists, but in another portion of the lung; and they are mutually dependent upon each other.

We have already noted that fibrosis is often found in the lower and posterior portions of the lungs and that emphysema is found predominantly in the upper and anterior portions.

If the fibrosis is a localized one in the upper lobes, due to infections such as tuberculosis or other chronic diseases, then emphysema is also found, first in the neighboring lung areas, but also in distant points if the fibrotic process is extensive enough. The same condition of affairs is found in pneumonokoniosis and in vascular fibrosis, both of which are invariably associated with emphysema.

Such emphysema secondary to fibrosis may be of the compensatory type and reversible. But if long continued, the condition becomes irreversible and true permanent emphysema results as the retraction power of the lung fails.

On the other hand, if the emphysema is the primary and predominant condition, situated, as we have seen, mainly in the anterior upper lobes, then the hyperexpanded lung exerts pressure upon the other lung areas and bronchial drainage function in them is impaired and fibrosis results. These changes are most regularly found in the posterior and lower lobes.

So, we thus find these two conditions going hand in hand as the accompaniments of all chronic lung disease, and we can therefore think of them

no longer as two absolutely distinct diseases but rather as one combined clinical entity which we may term, in general, chronic lung disease.

The Clinical Picture of Chronic Lung Disease

In the early stages of these conditions there may be no symptoms or other clinical manifestations even though the underlying basic changes may already be quite definite and considerable, as was pointed out in our consideration of the pre-clinical forms of pulmonary fibrosis. When the changes are sufficiently advanced both in tissue and functional pathology, then certain symptoms present themselves.

Symptoms. These symptoms are most regularly cough, expectoration and dyspnea. When the disease has become so advanced as to seriously impair cardio-respiratory function, then cyanosis also appears, and when the basic conditions of fibrosis and emphysema are associated with or dependent upon bacterial infection, then we usually have also fever with its accompanying systemic symptoms.

Of all these various symptoms the characteristically important one from the standpoint of function is *dyspnea*, and it is this symptom which most regularly and constantly brings these conditions to our attention clinically.

The recent studies of dyspnea, which Drs. Cournand, Brock, Rappaport and Richards [8] have been making, are of considerable interest, as they appear to demonstrate that dyspnea in these cases of fibrosis and emphysema is not due to chemical changes in the blood but rather to the failing coördination in the neuromuscular apparatus of respiration. This new concept of dyspnea as a subjective sensation referred to the breathing apparatus places the responsibility for its causation upon failure of lung function, and may be most helpful in furthering our knowledge of functional pathology of chronic lung disease.

Physical Signs. From the standpoint of examination, while the physical signs may be varied and frequently quite marked, it is well known that they are very often not characteristic and that the associated presence of fibrosis and emphysema in the lungs tends to modify and obscure such physical signs as may be characteristic if either condition be present alone. We therefore find that physical examination is of comparatively subordinate importance.

Roentgenological Signs. The most fruitful source of information is the roentgenogram. But here also we encounter practical difficulties similar to those described with physical examination, and for the same reason, namely, the tendency of associated emphysema and fibrosis to mutually obscure each other. Roentgenologists have noted the fact that with the ordinary routine technic it has often been difficult to obtain a correct pathological interpretation of the roentgenogram of these combined conditions; but the true significance of this fact is often not recognized. Even profound students of roentgenology do not as yet thoroughly understand the physical and optical laws which underlie this reaction, the effects of

which however are obvious. For example, the liver, normally densely opaque to the roentgen-ray, may become translucent when a large loop of bowel distended with gas overlies it, or the filtration effect of the bony rib makes obvious a density in the underlying lung, which same density is invisible in the intercostal spaces by the same ray, or again extensive fibrotic processes in lung or pleura obscure underlying cavities in the ordinary roentgenogram, which can easily be brought out by special procedures and different penetration. This being so, it is easily understandable how fibrosis, which produces increased densities, and emphysema, which is associated with increased air content, would not only very definitely affect the roentgenological picture in themselves but also have mutually important influences upon each other. Therefore it is of great practical importance to appreciate the limitations of the roentgenological method of examination in the interpretation of pulmonary lights and shadows in terms of definite pathological conditions, unless special technical precautions are taken to avoid error.

Such thorough students of the subject as Pancoast and Pendergrass [9] in silicosis and Fray [10] in emphysema, have done much to increase our roentgenological knowledge of these conditions. But they too have recognized the limitations and possibilities of error in roentgenography. In the cases of silicosis, Beintker,[11] who has recently studied this subject thoroughly both from the roentgenological and functional standpoint, has definitely come to the conclusion that the evaluation of the functional disturbances, particularly as evinced by dyspnea, is the more important and valuable method of study.

Functional Tests. We therefore find a demand gradually asserting itself for some clinically applicable measure of pulmonary functional impairment. Such a measure of function should aid not only in detecting the presence but also in estimating the severity of such conditions as fibrosis and emphysema of the lung. It should be of assistance not only in determining the extent of the lesions but particularly in assessing the degree to which each patient has achieved a functional adaptation to his pulmonary damage.

Slow progress is being made in attempts to devise laboratory or clinical functional tests which will be of assistance to our understanding of these and similar diseases. Up to the present time it must be admitted that the value of these tests is somewhat limited and that the conclusions to be drawn from them must still be considered to be of a tentative nature. It may be of interest, however, to review a few of the tests which are being employed by workers in this field.

It would appear that such functional studies might be of the greatest importance in the question of prognosis, for extraordinary variations in tolerance to apparently similarly extensive disease are found. Also they may afford an opportunity to discover constitutionally predisposed individuals and to remove them from untoward conditions of work or other environment before advanced and debilitating disease has resulted. Finally, in the now rapidly growing field of thoracic surgery for various chronic

diseases these tests may afford a basis for better selection of suitable operative risks and point the way to appropriate measures to meet emergencies which may arise during or after such operations.

Some of the more usual functional tests are as follows:

Functional Tests of the Lungs

I. The study of the statics and dynamics of the breathing apparatus.

A. The determination of lung volumes.

The purposes of this study are:

1. To measure the volumes of air available for normal breathing (tidal air) and for extreme breathing (vital capacity and its two components, complementary air and reserve air).
2. To measure the volume of air which is constantly present in the lungs and in which the mixing of the gases takes place (residual air).

The graphic method is the best for recording the vital capacity.

The determination of the residual air is based upon the method of mixing of a known gas, derived from the work of Van Slyke and Binger. For clinical purposes Christie has described a method whereby oxygen is used as a mixing gas. Hurtado et al. have published statistical studies in normal, emphysematous and fibrotic cases. They emphasize the relationship between the different components of lung volumes on the one side and the total capacity on the other, and they furnish numerous data as to the variation in the different ratios in pathological cases. The graphic registration of lung volumes, either alone or in connection with a parallel study and recording of pleural pressure, as proposed by Koontz and Meakins and Christie, provides valuable information concerning the elastic state of the lungs.

Although the employment of this method of study of lung volumes is widespread, the warning is justified that conclusions from such studies should be submitted to rigid criticism. First, because the method of estimation of the residual air is based on the assumption that mixing in the lungs is quite homogeneous, which in cases of emphysema is far from true. Richards, Cournand and Larsen have recently undertaken studies to determine the limits of error in this method and the possible corrections to be used. And, secondly, because the study of the vital capacity

measures the maximum volume available for breathing purposes without any reference to the power of endurance, in other words without taking into account the efficiency of the functioning breathing apparatus.

B. Spirometry.

This method has a great advantage in fulfilling the above requirement, namely, the measurement of the efficiency of the functioning breathing apparatus. It is simple, physiological, and based upon the recording of the breathing upon slow and rapid moving drums, with reference to time. The rate and depth of the breathing may be easily studied on the graphs, as well as the form of each breath, the slope of the curve, especially the end of each phase, the pause, the variation of the level of the resting position. Indirectly also this method permits estimation of the speed of the airflow, which is related to the state of the air passages and the dynamics of the breathing apparatus (diaphragm and moving chest cage). The use of adrenaline injection, by modifying the state of bronchial resistance permits a better analysis of the phenomena.

Maximum voluntary breathing in a standard time should also be recorded and studied on the basis of the volume of each breath and the volume of air breathed per second, and compared with the vital capacity tracings.

It is to be hoped that the pneumotachographic method invented and developed by Fleisch may become available for clinical purposes, as it registers directly the change in the speed of the airflow and at the same time the form of the breathing.

II. The study of the lesser circulation.

A. Venous pressure.

The best physiological method available is the direct method of Moritz and Tabora. The position of the right auricle which determines the zero point for the measure of venous pressure being quite variable according to the distention of the thoracic cavity in emphysema, lateral roentgen-rays of the chest should be taken. The variation of the venous pressure should be recorded in connection with the phase of respiration and its variation of amplitude, thus affording information concerning the dynamics of the venous return to the chest.

As an index of the ease with which the blood passes through the large veins, right heart and pulmonary vascular bed, an elevated venous pressure indicates increase of resistance somewhere in the vascular path. Despite reports in the

literature to the contrary, in moderate and advanced emphysema the venous pressure is often normal or even abnormally low.

A recent test associated with the measurement of venous pressure has been devised by Caughey to estimate the capacity of the heart and of the pulmonary vascular bed to take care of an added load of fluid infused in a standard time. This test has a practical value for determining the individual case in which saline infusion or blood transfusion may be indicated or contraindicated, particularly after surgical operations.

B. Blood velocity.

This is a measure of the linear velocity of the column of blood through a known segment of the circulatory system, including the whole lesser circulation. The path goes from the antebrachial vein through the right heart and the vascular bed of the lungs, ending in different parts of the arterial system, according to the method employed. The cyanide method, whereby the gasping reflex is set up when the head of the column of blood carrying the cyanide reaches the sinus carotides, seems to give the most definite end-point.

As the various parts of this system are subjected to variable influences whenever pathological conditions are present in the lungs, efforts have been made to isolate smaller portions, for instance from the antebrachial vein to the alveolar area, by using intravenous injections of ether. The reliability of this method is still doubtful.

In fibrosis and emphysema the blood velocity throughout the whole system is usually above the upper limits of normal.

C. Cardiac output.

The measure of the cardiac output or minute volume of blood passing through the lungs is based on methods involving either the Fick principle whereby mixed venous blood CO_2 is equilibrated with a known mixture of CO_2, or ventilation of foreign gases (Grollmann).

As far as we are aware, the poor and uneven diffusion of gases through the lungs in cases of emphysema, limits the applicability of these methods.

III. The study of the physico-chemical state of the arterial blood.

A. Arterial puncture.

This is definitely a clinical method of investigation and affords unique information as to the O_2 saturation, CO_2 content and pressure, level of the CO_2 dissociation curve, pH, etc., but it requires accurate analysis by the Van Slyke-Neill manometric apparatus. It brings out the integration of the three

main factors, namely, ventilation, diffusion of the gases, and perfusion of the lungs.

Clinically it gives indications as to the advisability of O_2 therapy and enables one to follow its action.

B. Alveolar samples.

The analysis of alveolar samples of air is not a substitute for the previous method, particularly in emphysema and fibrosis. The uneven specimens obtained in these conditions, the poor approximation of the arterial CO_2 per cent and the alveolar CO_2 per cent, are good proof of the variability of the ventilatory condition prevailing throughout the lungs in these diseases.

IV. The study of the total ventilation.

The measure of the total ventilation with the Tissot apparatus and the estimation of the O_2 intake and the CO_2 output determines the metabolic rate of the body and the level of ventilation required.

V. Exercise tests.

In recent years the value of the duplication of most of the above tests during exercise has been emphasized. In the hands of various workers the type of exercise varies, from stepping up and down stairs, to a fixed task performed on a bicycle, with the recording of the work done in terms of kilowatts. Whatever method is used, it seems that the form of exercise should produce conditions under which the patient is able to feel the strain, and it should be most flexible. It is under conditions of actually increased tissue demands that the efficiency of the breathing apparatus should be tested.

Special attention should be given to the form, amplitude, rate of breathing, total ventilation per period of time, O_2 intake, arterial saturation, and finally to the level of the CO_2 dissociation curve. These data should be observed during the recovery as well as during the exercise period.

In general, it should be emphasized that none of the functional tests should be interpreted separately, neither should they exclude other clinical data, particularly linear chest measurements, and observation and recording of the chest and abdominal walls, either by simple inspection or with the help of the fluoroscope or roentgenogram.

Among the very numerous functional tests which have been suggested, the above have been chosen as the most practical and they are the ones that are being used routinely in the functional study of chronic pulmonary disease in our Service in Bellevue Hospital.

These and other methods are the type of studies which are beginning to be developed and which will certainly play an increasingly important part in the clinical study of various lung diseases.

Clinical Classification

For practical purposes the clinical evolution of chronic pulmonary disease may be separated into three phases:

1. *The Bronchial Phase.* It has already been brought out in our discussion of the pathogenesis of fibrosis and emphysema that the primary cause has been found to lie in the air passages, so that in the earlier phases, while the process is mild and well compensated, it remains localized in these passages. There may be temporary or localized pulmonary congestion with interference of drainage function, which manifests itself by a group of symptoms usually attributed to bronchitis. We also see these changes going over into chronic persistent bronchial catarrh, frequently associated with allergic asthmatic paroxysms in predisposed individuals. This predominantly bronchial phase may persist for a long time before a definite or marked change in lung function occurs.

The recognition of the importance of this bronchial phase as the forerunner of serious lung disease has already been emphasized, and from a clinical point of view it would appear that this is the phase in which properly directed protective measures might control the development of serious disease. Effective preventive treatment of cases at this stage in time might considerably diminish the prevalence of the more serious lung conditions, fibrosis and emphysema.

2. *Pulmonary Phase.* Sooner or later if the bronchial condition persists, general lung function shows increasing signs of embarrassment which requires definite compensatory effort, and then the clinical picture takes on the aspect of real pulmonary disease. In the literature we find this phase described either as chronic emphysema and bronchitis, or as chronic pulmonary fibrosis associated with bronchitis or bronchiectasis, or as a combination of these conditions, with or without specific associated infection as in tuberculosis. For, as is very evident, the transitions and interactions of these conditions from one to another are very fluent.

3. *Respiro-Circulatory Decompensation Phase.* As the conditions persist and advance, increasing respiro-circulatory embarrassment is evident, and then cardio-circulatory compensatory effort becomes a conspicuous feature of the clinical picture. Hence, we may call this phase the respiro-circulatory decompensation phase. It is extremely important to recognize the interdependence of the respiratory and circulatory function in advanced pulmonary disease. Yet in the later stages the interaction is so confused that it is frequently difficult to state whether the symptoms presented are due mainly to respiratory or, on the other hand, to circulatory decompensation. This interacting relationship between cardiac and respiratory function in chronic lung disease has been very brilliantly brought out by Castex and Capdehourat [12] in their study of that most interesting condition known as Ayerza's disease. While it is often extremely difficult to assess the relative importance of the respiratory and circulatory function, from the

clinical point of view the important thing to emphasize is their close interaction, and to realize that in the end-stages of chronic pulmonary disease failure of function in both of these vital systems may develop.

Intrinsic Lung Function

Having presented pulmonary fibrosis and emphysema as the fundamental bases of all chronic lung disease, and having attempted to interpret these conditions as essentially disturbances of function, I wish, in conclusion, to suggest the consideration of a hypothesis which may aid our further thinking along these lines.

For several years Dr. Rappaport of our staff has clung to the conception that there must reside in the lung a power of prompt adaptation to the changing demands upon respiration, which power cannot be adequately explained by the prevailing concepts of the lung as a simple mechanically elastic organ. Evidence is apparently accumulating in favor of some such conception, which we may designate tentatively as intrinsic lung function.

In our discussion of compensatory emphysema we called attention to the fact that over a century ago Laennec recognized pulmonary hypertrophy as distinct from emphysema, and that Célice has recently repeated these observations.

More recently still, Hilber [13] has offered some very convincing experimental evidence in rats, demonstrating that following the extirpation of one lobe of the lung, the remaining lung areas compensate for the loss not only by ballooning-up, that is, by compensatory emphysema, but also by genuine regeneration with new formation of perfectly efficient lung tissue with corresponding new bronchi, new vessels and new respiratory alveoli.

The increasing vogue of lobectomy in the surgical treatment of various lung conditions should in the near future offer important histological evidence concerning the occurrence of such regeneration of lung tissue in human beings, and clinically there is already some evidence in its favor from the fact that following lobectomy the remaining portion of the lung comes to replace most of the space formerly occupied by the excised lobe, without however the occurrence of the usual evidences of emphysema. As far as I am aware, however, no histological evidence is as yet available in cases where these conditions have existed a sufficiently long time, to determine whether or not true lung regeneration has occurred.

Hilber believes this regeneration to be dependent in some way upon changes of air currents produced by the extirpation of the lobe.

This evidence is new and important, but still such regeneration takes some time, and readjustments of function would appear frequently to take place more promptly than can be entirely explained by this regenerative process. In this connection Orsós [14] has however, also very recently, in his studies of the respiratory epithelium, reported upon histological evidence of a remarkable continuous change which goes on over the breathing surface of the lung.

We offer the hypothesis that perhaps these experiments as well as clinical evidence suggest the possibility that the breathing surface represents an extraordinary surface structure of the body, which can adapt itself to its unique task by so rapid and constant a change of its elements as to enable it to retain its extreme delicacy in spite of its vast exposure to damaging influences, and at the same time to retain its adaptability to the great strain of constant respiratory and circulatory movements.

If some such theory could be sustained, it would be of outstanding importance in the solution of many vexing problems.

We do not, however, need to resort to the hypothetical in order to emphasize the importance of functional pathology in the study of lung diseases.

The field is difficult but extremely fascinating, and we have as yet advanced only to the threshold of our knowledge of it. Continued scientific and clinical research will make for progress which it will well repay us as clinicians to follow with keen interest and appreciation if we are properly to understand many of the intricate problems of chronic lung disease.

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ETIOLOGY OF THE PULMONARY FIBROSES AND MEDICO-LEGAL ASPECTS OF PNEUMONOKONIOSIS *

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The medico-legal questions which have arisen in connection with the pneumonokonioses are of two kinds: those which come from common law suits for negligence, and those which are connected with workmen's compensation laws. Many of our states have not yet included pneumonokoniosis in their compensation schedules. In these states a furious battle is being fought in the courts, into which medical men are being drawn by both sides. The physician who is suddenly projected into the "no man's land," which is the territory of the expert medical witness, finds himself between two fires. He is faced with ethical problems of the greatest complexity, bewildered and entangled by the barbed wire maze of legal technicalities, apt to fall in the slippery mud of legal chicanery. It is the aim of the writer, on this occasion, to attempt to find the way by means of which the medical man may extricate himself without dishonor. He must not, however, be content with this negative virtue. He must go farther in a positive direction in an effort to mold and guide legal ethics, and to aid in setting up new laws and procedures for the better establishment of equity. He must aid and guide industry in limiting at the source the causes for legal action.

In a negligence action the plaintiff should be required to prove two things: first, that he has sustained an injury; second, that this injury is the result of the negligence of the defendant. In such actions the medical witness may play one of two rôles. He is most frequently called upon to contribute his opinion as to whether or not an injury has been sustained. In rare instances he may be qualified to give expert opinion as an industrial hygienist or sanitarian on the question of negligence. Too frequently a medical witness is permitted to give an opinion on the question of negligence when he is inadequately qualified to give it. Most of the ethical difficulties of the medical witness can be eliminated if he will observe two rules: first, to refuse to give an opinion on matters which lie outside the field of his actual experience as an expert; second, to refuse to give an opinion on a hypothetical question in which the premises or assumptions are insufficiently exact to warrant the formation of a conclusion.

When the medical witness is called upon for an opinion as to the nature and extent of injury to the lungs which may be attributed to the inhalation

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

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of dust, there is available for his guidance a considerable amount of accurate information (Klotz [11]). The work of the experimental pathologists has given a clear picture of the evolution of pulmonary fibrosis resulting from exposure to dusts of various kinds, with accurate specifications as to concentration, duration, particle size, etc. Similarly certain industries, notably that of gold mining, in which fairly pure silica is the principal noxious agent, have had a health hazard which can be rather specifically defined. The injuries sustained in these industries result eventually in a fairly clear-cut nodular fibrosis, which presents a highly characteristic appearance to the pathologist or roentgenologist. The "ambulance chasing" lawyers, however, have not confined their attention to these highly specific injuries. Suits are filed against industries in which dusts of all kinds are found, organic as well as inorganic. In many of these industries the nature of the dust hazard has not yet been clearly defined. Work in progress in many centers indicates that the hazard varies tremendously, that some dusts are not only quite innocuous, but even protective in their action as in the case of gypsum, sea coal, aluminum oxide and certain clays (Gardner [5, 6]).

The plaintiff's attorney is very rarely able to adduce evidence either of the quantity or composition of the dust, or of the particle size. The dust is usually described in vague and general terms. Statements are given as to its effect on the visibility of objects in the room, the amount settling out, on clothes, face, machinery, beams, etc. In consequence when the plaintiff's case is complete the assumptions in hypothetical questions based upon it are frequently inadequate to justify an opinion as to the competency of the conditions described to produce the injuries alleged to exist.

The defense in these actions may or may not possess data as to dust counts, petrographic and chemical analyses, roentgen-ray spectrum analyses. When these data are available they are sometimes suppressed. There is rarely time, in the preparation for trial to submit the question to the experimental pathologist for settlement. In such cases some indication of the pathogenic possibilities in a dusty trade, concerning which other data are lacking, may be obtained by making a roentgen-ray survey of the men employed in it. For instance, roentgen-ray examinations were made of the chests of 673 men applicants for reëmployment, of whom 156 were foundry men and 517 a general group of industrial employees including some workers having had dust exposures of a hazardous nature, such as enamelling, sand blasting, chipping and grinding, but a majority of the general group were not exposed to recognized dust hazards. The following is a crude analysis of the findings in this group:

Group	Foundry		Non-foundry	
	No.	Per Cent	No.	Per Cent
Total	156		517	
Pneumonokoniosis	21	13.46	22	4.25
Active pulmonary tuberculosis	4	2.56	7	1.35
Healed pulmonary tuberculosis	11	7.05	39	7.54
Non-tuberculous respiratory infections	16	10.25	86	16.63
Other abnormalities	22	14.10	62	11.99
Normal	82	52.54	301	58.20

From the foregoing figures it is quite apparent that pneumonokoniosis develops in a considerable number of foundry workers after long exposure, in the foregoing series after an average employment of about 17 years. Our experience leads us to believe, however, that the dust hazards in a foundry are not so great as those which exist in some other industries or occupations (gold mining, sand blasting). This may be due to the fact that dust concentrations are not so great, or to the admixture of other constituents in the dust which modify the action of pure SiO_2. Against the 17 years required to produce pneumonokoniosis in a foundry we can compare the 9 to 12 years required to produce silicosis in the gold miners of South Africa (Fraser and Irvine [4]). While the figures show a definitely greater incidence of active tuberculosis in this group of foundry workers as compared with the larger general industrial group our experience does not indicate that the tuberculosis hazard in foundries is nearly as great as that reported for some of the other dusty trades. We have observed not infrequently the healing of tuberculosis in men during the earlier stages of foundry pneumonokoniosis. It is true, of course, that tuberculosis tends to become inevitably progressive in the nodular stages. Lanza and Vane [12] give statistics which show that the general mortality of foundry men is 55 per cent above the expected, and their mortality from tuberculosis 79 per cent above the expectancy; but these figures are low when compared with those of gold, silver, lead, zinc, and copper miners among whom the mortality from tuberculosis is from 8 to 18 times the general expectancy.

Collis and Yule [3] present a most startling comparison of the general mortality experience in a group of workers in silica dust with that of a standard population and a group of workers not exposed to silica. Their analysis shows not only a great excess mortality from tuberculosis and all other respiratory diseases among the silica workers, but an extra mortality from such apparently unrelated causes as cancer, cerebral hemorrhage, cirrhosis of the liver and valvular heart disease as well. These findings lead Collis and Yule to the conclusion that "silica is such a body poison as is lead, even though it exerts its maleficent influence, especially with regard to tuberculosis, mainly on the respiratory organs through which it gains access to the body."

Such general statements in regard to the most severe silicotic injuries, when placed before a jury may give quite an erroneous impression of the seriousness of the hazard in the foundry industry or in gypsum miners or in other dusty occupations in which the health hazard is relatively small. Data of the sort introduced by Lanza and Vane [12] are of the utmost importance to the medical witness in forming his opinion as to the competency of a given exposure to produce the injury claimed. The witness must on the other hand keep clearly in mind that the common law suit deals with an individual case, and not with a whole population submitted to analysis by an actuary.

The relationship of non-tuberculous infections to dust in the production

of pulmonary fibrosis is not as clear as that of tuberculosis. One reason for this, no doubt, is their lack of specificity and the difficulty of producing or controlling them in experimental animals. From the studies of McConnell and Fehnel [14] and Collis and Yule [3] it appears that the death rates for all non-tuberculous infections are higher among workers in siliceous dusts

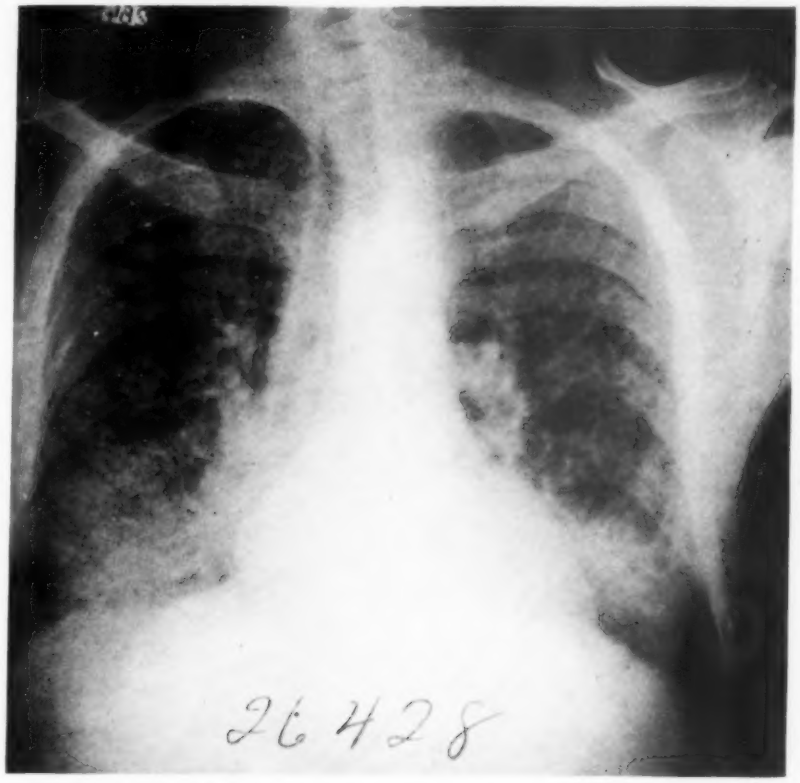

FIG. 1. Roentgenograph made of the lungs of S. B., October 12, 1929, during the second attack of acute respiratory infection. He had been employed as a sandblaster from 1920–1929.

than in the general population. In the roentgen-ray survey of 673 men to which we have previously referred, that type of fibrosis of the lower portions of the lungs such as is commonly seen in individuals suffering from chronic bronchitis or chronic upper respiratory infections, occurred more commonly in the non-foundry group. The number of men in the survey is too small to make the figures absolutely reliable. They suggest, however, that the worker in silica more frequently succumbs to acute pulmonary infections instead of surviving with chronic infections producing fibrosis.

Proske [17] has presented a bacteriological study of some of the non-tuberculous infections occurring in pneumonokoniosis, dealing largely with the anaerobic fuso-spirillar organisms.

An interesting case illustrating the rôle played by a recurring non-tuberculous infection in the evolution of a nodular fibrosis is that of S. B., a man of 52, who was employed during the years 1920–1929 as a sand-blaster in a stove factory. Beginning in the spring of 1929 he had the first

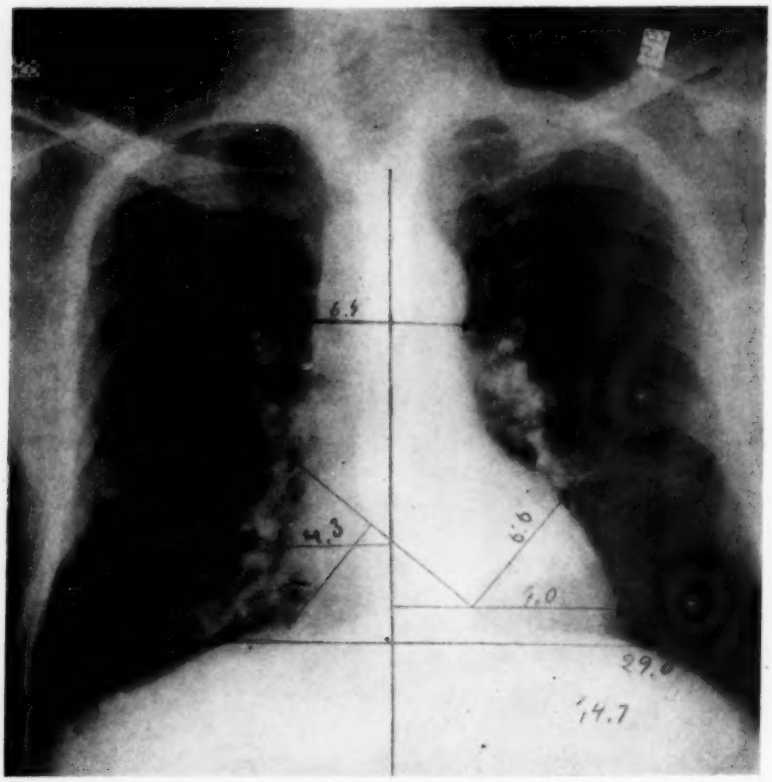

FIG. 2. Roentgenograph made one month after figure 1, the signs of infection having subsided.

of a series of severe respiratory infections with fever, leukocytosis, purulent sputum. In October 1929 he had the second attack of this type. The roentgenograph of his chest at that time is shown in figure 1, revealing diffuse soft nodular shadows in both lungs with dense confluence at the bases. Figure 2 shows the roentgenograph made one month later when the infection had subsided and all physical signs had disappeared. The roentgenograph reveals only a diffuse increase in the perivascular peribronchial markings with the faintest suggestion of nodulation. In January 1932 a third attack of acute respiratory infection occurred. In figure 3, the roentgenograph reveals dense shadows of consolidation in both lower lobes. Figure 4 is the roentgenograph made in October 1934 during an interval of freedom from evidences of infection. It reveals a considerable increase in the density of the peribronchial perivascular shadows and dense shadows in both hilus regions and right base.

In January 1934 the roentgenograph shown in figure 5 was made during an interval of freedom from acute infection. This shows an increase in the nodular shadows diffusely distributed through both lungs, though more dense in the bases.

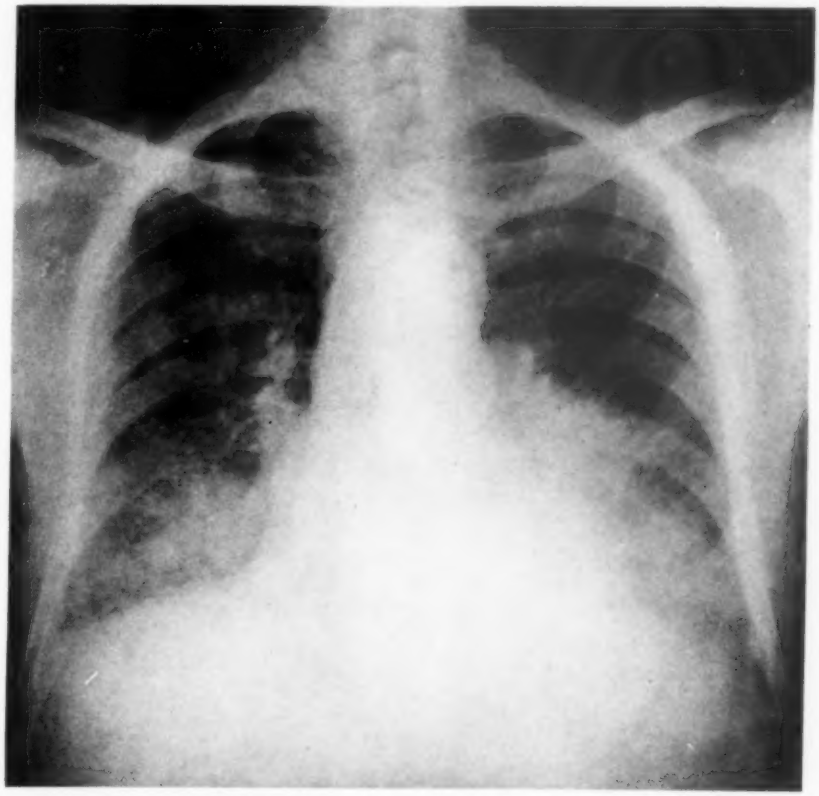

FIG. 3. Roentgenograph made of chest of S. B. on January 9, 1932, fourteen months after figure 2, during third attack of acute respiratory infection.

In March 1934 another attack of pneumonia occurred. Figure 6 reveals a dense area of consolidation at the right lung base.

In March 1935 the patient was free of acute respiratory infection. The roentgenograph (figure 7) made at that time reveals a diffuse nodular fibrosis consistent with a diagnosis of silicosis. The evolution of this fibrosis occurred over a period of six years, during which four separate attacks of bronchopneumonia occurred. In each attack repeated examinations of the sputa failed to reveal tubercle bacilli.

If this case were in litigation, with only the occupational history, clinical and roentgenological findings upon which to base an opinion, a diagnosis of pneumonokoniosis complicated by chronic respiratory infection could be made with "reasonable medical certainty." Such an opinion might be modified, however, if an autopsy were performed, in which sections were

subjected to micro-incineration by a technic such as that of Irwin [10] in addition to the usual stained preparations. The data should also include chemical study of the ash of the lung. McNally [15] has collected data on ash analyses from the literature and his own findings, which show that a value

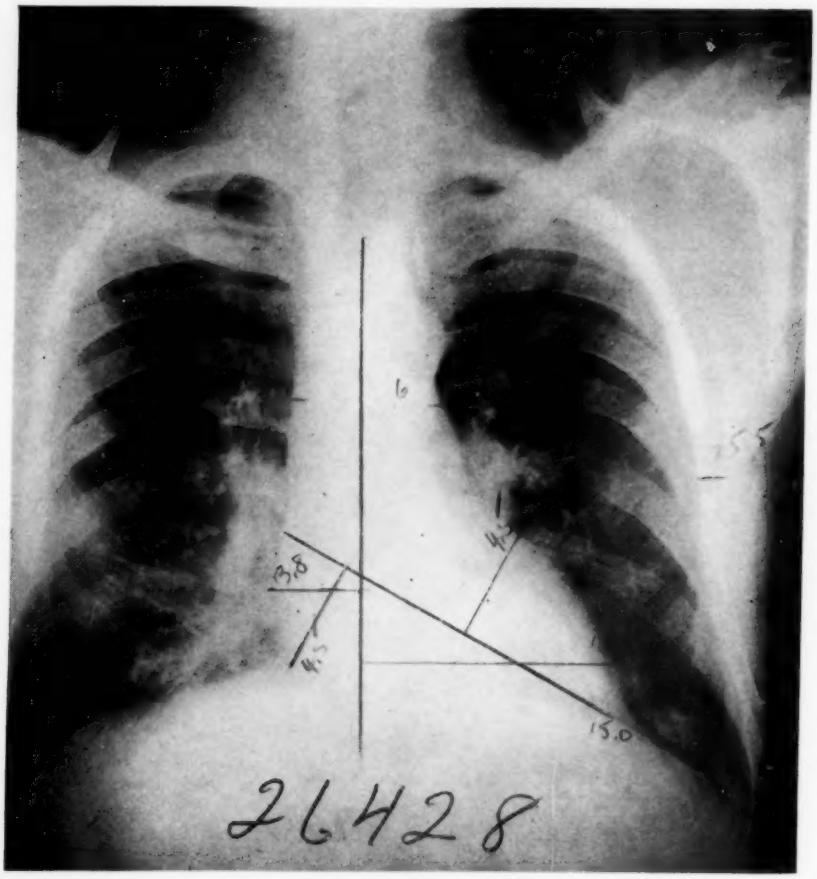

FIG. 4. Roentgenograph of chest of S. B., made October 24, 1932, during a period of quiescence of infection.

of more than 2 mg. SiO_2 per gram of dried tissue indicates undue exposure to dust. Silica determined chemically in this way may have been derived in part from silicates. For this reason chemical analysis of the ash should be supplemented by petrographic examination, and in addition to roentgen-ray spectrum analysis as described by Bale and Fray,[1] which gives a roughly quantitative estimate of the amount of free silica and of the silicates present.

The medico-legal problems of pneumonokoniosis under Workmen's Compensation are very different from those of the common law. In the Province of Ontario and in Wisconsin compensation may be adjusted to the degree of disability incurred. The problem of finding a yardstick for

the measurement of disability has been under active investigation at the University of Rochester for three years, and it is still far from solution. From observations of the pulmonary capacity and its subdivisions, and of the ventilation during exercise [7, 8, 13] we may say that simple fibrosis comparable

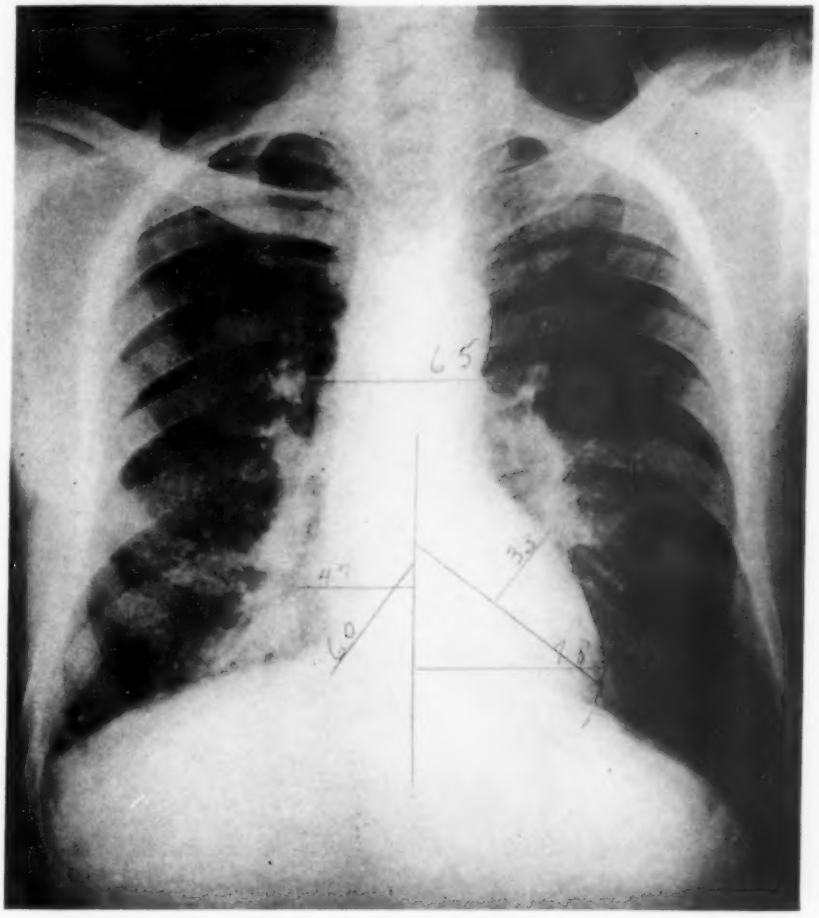

FIG. 5. Roentgenograph of chest of S. B., January 1934, made during a period of freedom from infection. Nodular fibrosis has become more distinct.

to the primary stage of simple silicosis is not disabling. In the second stage of uncomplicated nodular fibrosis, there is practically speaking no disability for ordinary manual work if allowance is made for age. In our observations the subjects with nodular fibrosis had an average age of 47, while that of the normal controls with which they were compared was 23 years. If emphysema is added to the fibrosis, either by the intercurrence of asthma or in compensation for the shrinkage of a part of the lung in dense fibrous agglomerations, disability is greatly increased. It may fairly be

rated at 100 per cent when the residual air reaches 50 per cent of the total capacity.

The demonstration of active tuberculosis at any stage should justify the award of compensation for total disability. In the case of primary pneu-

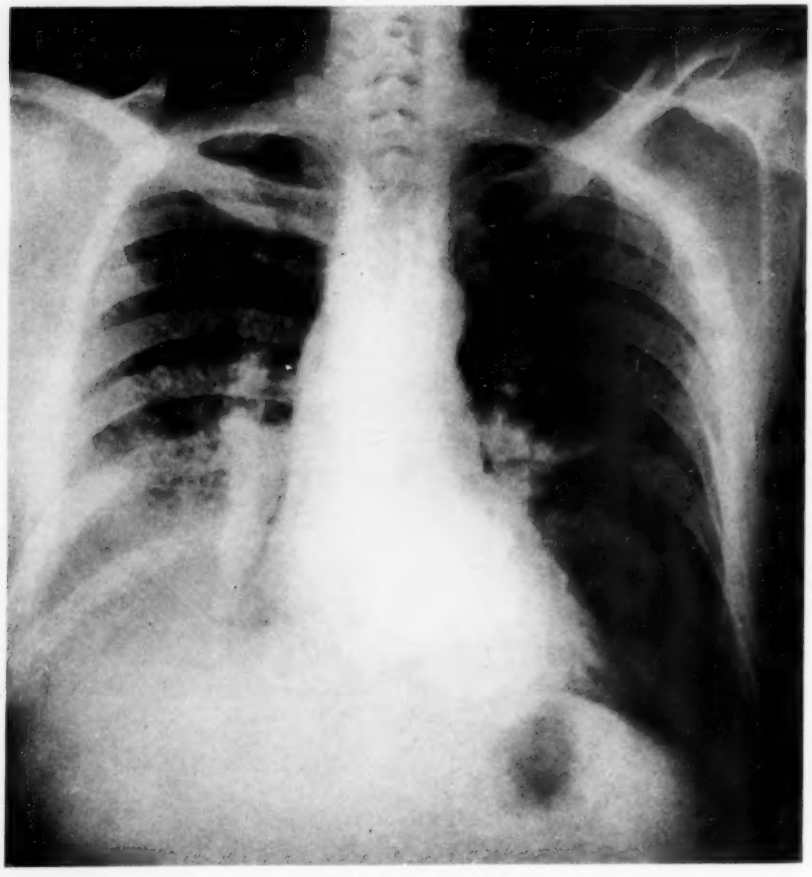

FIG. 6. Roentgenograph of chest of S. B., March 1934, during the fourth attack of acute respiratory infection, five years after the first attack.

monokoniosis of foundry workers, or iron miners, this may not be permanent, as tuberculosis may heal in this stage under appropriate treatment.

In the age groups in which pneumonokoniosis is most frequently found, cardiovascular disease becomes increasingly frequent, and such disease may contribute to the production of dyspnea. When this factor is detected by the clinical or electrocardiographic examinations it is impossible to determine the relative contributions of respiratory and cardiac lesions to the disability. However, if the viewpoint of Collis and Yule [3] is accepted, namely, that silica is a general body poison as is lead, the differentiation between the two causes of respiratory disability, when they coexist, becomes less important

in achieving equity in compensation awards. This would be true particularly if cognizance were taken only of the extra hazard due to the occupation, so that compensation for complete disability were awarded in the ratio

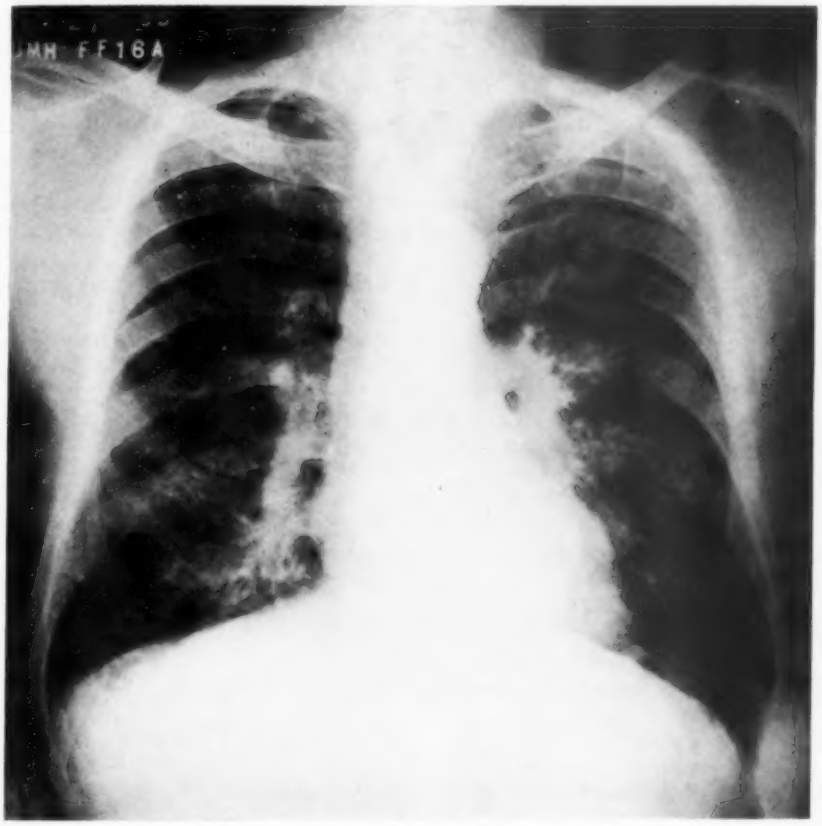

FIG. 7. Roentgenograph of chest of S. B., March 1935, six years after the onset of acute respiratory infections, during an interval of freedom from acute symptoms.

of the extra mortality above standard expectancy to total mortality for the workman's age group in his particular occupation.

CONCLUSION

In this rambling discussion I have endeavored to show the complexity of the medico-legal aspects of pneumonokoniosis which makes it so difficult to secure equity under the common law in negligence actions. Pure pneumonokoniosis probably does not exist outside of laboratories. The fibroses of the lungs of workers in dusty trades are probably the result of a combined action of dust and of infection, non-tuberculous as well as tuberculous. It is extremely difficult to establish the responsibility for negligence in individual cases. Equity is more likely to be achieved through workmen's com-

pensation under a general occupational disease law in which awards are adjusted to the degree of disability.

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TREATMENT OF CHRONIC RHEUMATOID ARTHRITIS; FURTHER OBSERVATIONS ON THE USE OF STREPTOCOCCAL VACCINE*

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IN a previous communication I [1] have reported the results of attempts to confirm the blood culture studies of Cecil, Nicholls and Stainsby [2] in cases of chronic rheumatoid arthritis. The technic of these investigators was followed in detail except for two minor variations which were devised to lessen the chances of contamination. In but a single instance were streptococci recovered from either the blood stream or the joint fluids so cultured. These results did not substantiate those of Cecil, Nicholls and Stainsby and others, who report the presence of streptococci in the blood stream of 50 per cent or more of cases of chronic rheumatoid arthritis. They agree, however, with the observations of Dawson, Olmstead and Boots [3] and others, who failed to recover streptococci from either the blood stream or from joint fluid with sufficient frequency to be of significance. This lack of uniformity in the results obtained by different observers leaves us in doubt about the frequency with which streptococci occur in the blood stream of patients with chronic rheumatoid arthritis, and makes it impossible conclusively to maintain that the joint reaction in this disease is a focal or metastatic lesion. This does not mean that the streptococcus plays no part in the pathogenesis of the disease or even that it may not be the chief cause, but merely puts in question the manner in which the joint reaction is produced.

That the streptococcus is associated with chronic rheumatoid arthritis is indicated by the results of agglutination tests. Agglutinins for hemolytic streptococci have been found in the sera of patients suffering from this disease by all investigators who have searched for them. Dawson, Olmstead and Boots [4] found them in 67 per cent of 157 cases, in dilutions varying from 1 to 20 to 1 to 2560. Nicholls and Stainsby [5] found agglutinins for their "typical strain" in practically all patients with chronic rheumatoid arthritis. I have reported the study of 51 cases in which 46, or 90 per cent, showed agglutinins for hemolytic streptococci when tested against AB_{13}, a "typical strain" obtained from Cecil, Nicholls and Stainsby, and against the scarlet strain NY_5. Since this report I have increased the number of cases studied to 87. I have found that the same proportion gives positive results, having demonstrated agglutinins for AB_{13} and NY_5 in 79, or 90 per cent, of the 87 cases.

In a previous article I reported the occurrence of positive skin reactions in 55 cases of chronic rheumatoid arthritis tested intracutaneously with salt

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935.

solution suspensions of heat-killed streptococci. In these, 49, or 90 per cent, reacted maximally to a hemolytic strain, whereas only 6, or 10 per cent, gave the maximum reaction to a green strain. The number of cases tested for their skin reactions to streptococci has now been increased to 78. Table 1 gives the results and includes also the skin reactions in 11 cases of combined arthritis, 10 cases of hypertrophic arthritis and 3 cases of Still's disease.

TABLE I

Skin Reactions to Intracutaneous Injections of Hemolytic and Green Streptococci

	No. giving negative reactions	Reacting to 1 strain	Reacting to 2 strains	Reacting to 3 strains	Reacting to 4 strains	Reacting to 5 or more	Total
Rheumatoid Arthritis	3	14	8	13	15	25	78
Combined Arthritis	3	1	1	2	2	2	11
Hypertrophic Arthritis	4		1	2	—	3	10
Still's Disease	2		—	—	—	1	3

Cases of Chronic Rheumatoid Arthritis Showing	
Maximal skin reaction to hemolytic streptococci	69
Maximal skin reaction of viridans streptococci	6
No skin reaction	3
Total	78

Having demonstrated the strain of streptococcus among the many used to which a patient was most skin sensitive, this information was used as a guide to vaccine treatment. Twenty-eight patients with chronic rheumatoid arthritis received streptococcal vaccine intravenously at weekly intervals for periods varying from two months to over one year. The results of treatment were reported in the previous publication, and since then 17 additional patients have been treated. The present report will deal with the results of treatment in this group of 45 patients.

The group comprises 40 cases of chronic rheumatoid arthritis and 5 cases of combined arthritis in which the evidences of rheumatoid arthritis predominated. In every instance all foci of infection were removed and sufficient time was allowed to elapse to be sure that no benefit or further benefit was to be derived from the removal of the infections. The disease had been present for not less than 6 months, the average duration of all cases being 18 months, a sufficient length of time to justify classing them as chronic arthritis. Of the 45 patients, 30, or 67 per cent, have shown evidence of improvement; 15, or 33 per cent, have shown no clearly demonstrable improvement.

Because of the predominance of positive skin reactions to hemolytic strains of the streptococcus the vaccines which were used were prepared from hemolytic strains in all but two instances. Ten strains of hemolytic streptococcus derived from different sources were used. In 11 cases "Maith" strain obtained from a case of hemolytic streptococcus septicemia

was used; in 10 cases, NY_5, a scarlet strain; in 6 cases the " Lee " strain, obtained from a case of hemolytic streptococcus septicemia with acute infectious arthritis; in 6 cases AB_{13}, a " typical strain " furnished us by Cecil, Nicholls and Stainsby; in 3 cases " James," a scarlet strain; and in 3 " Cotton," a strain obtained from a case of hemolytic streptococcus septicemia. In one case each, " Evans," a scarlet strain, " Schmedes," " Altomare " and " Birge," strains from unknown sources, were used. The viridans strains used were " Tschetter," obtained from a knee joint, and " Waller " from an unknown source.

The patients have received weekly intravenous injections of vaccine prepared from the strain to which they had shown the maximal skin sensitivity. The initial dose was approximately 5 million organisms contained in 0.5 c.c. of vaccine. The dose was increased by 0.5 c.c., provided no constitutional reaction occurred. Febrile reactions were avoided by beginning with a small dose and increasing the dose sufficiently slowly. The increase in dosage was gauged by the patient's response and no set schedule of dosage was followed. In some instances fever did come on after the first few injections, but the subsequent doses were sufficiently reduced to prevent further reactions. Although no constitutional reactions occurred, as a rule the patients complained of focal reactions for about 24 hours after each injection. This reaction was manifested by increased pain in the involved joints, but after the reaction subsided the symptoms were usually improved. The improvement experienced always came about slowly, as a rule making its appearance in from four to six weeks after treatment was begun. In some instances it progressed more rapidly than in others, but often was not a steady improvement. From time to time during treatment joints have flared up but would often subside in a shorter time than was the patient's previous experience with exacerbations of such degree. In some cases definite improvement has been observed up to a point at which the arthritis seemed to become stationary, and beyond this point no further improvement was obtained. The benefit derived manifested itself by decreased pain, reduced swelling of the joints and surrounding soft tissues, and increased mobility of the joints. We have seen fusiform fingers diminish greatly in size and the swelling of other involved joints also decrease. In two instances improvement was in progress when the treatment was interrupted, in one instance because of the development of pulmonary tuberculosis with large hemoptyses, and in the other because of a cerebral thrombosis which produced a right hemiplegia. In both cases an exacerbation of the arthritis followed. Subsequently treatment was begun again and in each case improvement once more occurred. In the first instance much more improvement followed the second course of treatment than had followed the first; in the second instance an equal degree of improvement followed both.

Streptococcal vaccine was given intravenously to two patients suffering from active pulmonary tuberculosis. The increase in dosage was made very cautiously and constitutional reactions were entirely avoided. In both cases

the arthritis has improved during treatment and in one case improvement has been more striking than in any other case in the series. The pulmonary tuberculosis not only has not progressed but healing has gone on, and in one case the pulmonary lesion now is considered to be inactive.

During treatment the skin reaction to the strain used has regularly diminished in intensity and in most instances has entirely disappeared. Furthermore, agglutinins have appeared in the patient's sera for the strain employed, when not already present, and when present, as was the case with the hemolytic strains, the titre has materially increased during treatment.

One case improved during treatment to such an extent that the joints were considered inactive. Destructive change had not taken place. The previously affected joints appeared objectively normal and the patient was having no symptoms. The skin reaction, which originally was an area of erythema 2.25 cm. in diameter with a central area of induration of 0.5 cm., became quite negative. During treatment the patient had developed agglutinins for the strain used to a dilution of 1–5120. It seemed advisable to discontinue treatment. Three months later there was an exacerbation of the arthritic process and the sedimentation rate was then 51 mm. in one hour. Furthermore, the skin reaction to the strain used, completely negative three months before, now reappeared and was an area of erythema 1.5 cm. in diameter. Further treatment of this case has only just begun and we do not know what results may follow.

In all of the cases treated the sedimentation rate has been elevated, in some much higher than in others. The highest rate at the beginning of treatment was 54 mm. in one hour and the lowest was 15 mm. In 19 cases we have had the opportunity to follow the sedimentation rate during treatment and in this small series our observations have not been conclusive. In one of the most active cases, a man with every finger on each hand fusiform and inflamed and with both ankles actively involved, the rate was 17 mm. in one hour when treatment was started. There has been decided improvement in the ankles and the fusiform swelling of the fingers has diminished somewhat in size, yet the sedimentation rate has varied between 13 mm. and 22 mm. in one hour and is now 13 mm. In others the rate has steadily dropped with improvement as might be expected. This was observed in 12 instances. In others there has been an initial drop with a secondary rise, usually not to the original level, and in still others there has been no reduction whatever in the elevated sedimentation rate, although both subjective and objective improvement occurred. In the cases which have not improved the rate has not varied from its initial elevated level.

Fifteen of the 45 cases treated either have not improved or else the change which has come about has been so slight that improvement was questionable. In this group are three cases of combined arthritis; five cases showed longstanding and extensive change involving many joints; in seven cases we thought it reasonable to expect improvement but thus far none has come. In none of the cases has the arthritis been made worse

by treatment and no untoward reactions have occurred. In a few instances the urine has been followed after the injection of vaccine and in none has there been any evidence whatsoever of irritation of the kidney.

TABLE II

Cases Treated with Streptococcal Vaccine

	No. of cases	Improved	Unimproved
Rheumatoid Arthritis	40	28 (70%)	12 (30%)
Combined Arthritis	5	2 (40%)	3 (60%)

COMMENT

The attempt has been made to influence the joint reaction in chronic rheumatoid arthritis by the intravenous injection of streptococcal vaccine. This bacterial group was selected by reason of the universally demonstrated ability of the sera of chronic arthritics of the rheumatoid type to agglutinate hemolytic strains of streptococci. Just what this reaction may imply we cannot definitely say at this time but it cannot be entirely without significance. It is unlikely that natural agglutinins [4] would be so strikingly congregated as we find them in this type of arthritis, whereas they are found only infrequently in individuals suffering from other diseases and in normal people. I have found the reaction particularly useful in the differentiation of hypertrophic from rheumatoid arthritis and in establishing the existence of a rheumatoid arthritis when combined with hypertrophic arthritis. Keefer, Myers and Oppel [6] have shown that the agglutinating substances are contained in the proper globulin fraction of the serum and that they are true agglutinins. It seems to me that the almost uniform demonstration of this agglutinating property of the sera of patients suffering from chronic rheumatoid arthritis is the most convincing evidence yet produced to incriminate the streptococcus of playing a rôle in the etiology of the disease. On the other hand, Myers, Keefer and Holmes [7] have found that rheumatoid arthritis is not accompanied by an increase in the antifibrinolytic property of the plasma as is observed following proved hemolytic streptococcal infections and in rheumatic fever, and one hesitates to state emphatically that the presence of agglutinins indicates a causal relationship when the organism can be isolated so infrequently from patients with rheumatoid arthritis and when no other direct connection can be established. Just what the relation is must await further study. At the present time I am investigating whether or not the presence of agglutinins in arthritic sera for hemolytic streptococci is confined to human strains or can be demonstrated for the other groups of Lancefield's classification.

Since the agglutination of hemolytic streptococci occurred too frequently in this disease to be regarded as an accidental association we proceeded to test chronic arthritics for evidences of sensitivity to streptococci. We found that not only was the patient with this disease skin sensitive to streptococci but that this sensitivity was much more pronounced for hemo-

lytic streptococci than for green strains. Ninety per cent gave the maximal skin reaction to the former and 10 per cent to the latter. We have not compared this with the skin reactions of non-arthritics. We wished merely to learn to what strain of streptococcus the given arthritic was most sensitive when he showed agglutinins in his blood serum for hemolytic strains of this bacterial group. The demonstration of skin sensitivity does not of necessity indicate either a joint sensitivity or a general sensitivity, but in each case we have observed the skin reaction to diminish during treatment and in most instances to disappear entirely. The observation that the skin reaction reappeared in one case during a recurrence of symptoms after treatment had been stopped may be of far-reaching significance if this occurrence is found regularly under these circumstances.

In treating these cases we wished to see what relation might exist between the diminution of sensitivity to streptococci, as demonstrated by a decrease in the intensity of the skin reaction, and the manifestations in the joints. Not only has the skin reaction diminished during treatment but the agglutinating power of the patient's serum for the organism used has increased. In the cases showing improvement these changes have occurred concomitantly with improvement in the joints. We do not pretend to say that this relation establishes the specificity of the joint reaction. In the cases failing to show improvement under treatment there has been no difficulty in developing agglutinins or in raising their titre when a hemolytic strain was used, and in these the skin reaction also diminished. The benefit derived may be due to a non-specific reaction. We have, however, eliminated the febrile reaction, to which is commonly attributed the benefit resulting from the usual forms of non-specific vaccine therapy. We have attempted to desensitize the arthritic to the strain of streptococcus to which he showed the greatest sensitiveness. Furthermore, the strain used belonged to that group of bacteria for which the patient possessed agglutinins in his serum. And when this property of his serum indicates so definitely some relation of streptococci to his disease, although the nature of this relation is unknown, an alteration of this sensitivity could reasonably affect his arthritis. It is entirely possible that the steady increase in dosage is not necessary, but in all cases we have regularly increased the dose, keeping below the point at which constitutional reactions were produced. I do feel that the long continued use of vaccine is of value and have not hesitated to treat some cases for more than a year.

The group in which I have been able to follow the sedimentation rate is small but the results obtained are confusing. A diminution in rate with improvement or an unaffected rate in cases failing to show improvement would seem logical, but the bizarre findings would tend to cause one to doubt the value of the test as a guide to improvement. I have not found it necessary to resort to this test to determine whether or not improvement had occurred but have attempted to confirm the clinical evidence of im-

provement by its use. Certainly we are dealing with a test which is subject to many variables and we have thus far found it of doubtful value.

Summary

1. Seventy-nine of 87 cases of chronic rheumatoid arthritis were found to have agglutinins for hemolytic streptococci in their sera.

2. Seventy-five of 78 cases of chronic rheumatoid arthritis showed skin reactions to one or more strains of streptococci.

3. Sixty-nine cases, or 88 per cent, showed the maximal reaction to hemolytic strains, whereas 6 cases, or 7.7 per cent, showed the maximal reaction to viridans strains. Three cases showed no skin reactions to streptococci.

4. Thirty of 45 cases of chronic rheumatoid arthritis have shown improvement when treated with vaccine prepared from the strain to which they were most skin sensitive.

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GASTRIC ACIDITY IN CHRONIC ARTHRITIS *

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Achlorhydria and hypochlorhydria are frequently mentioned as accompaniments of chronic arthritis, but a search of the literature does not reveal any recent investigations of their occurrence in which the present technic including fractional analysis or the present standards of interpretation have been employed. There has, moreover, not been found any attempt to differentiate the gastric secretions in rheumatoid arthritis from those in osteoarthritis, although the present day division of arthritis into these two great groups would seem to make such a distinction of importance.

The object of this study was three-fold: to determine the gastric acidity in chronic arthritis by the fractional method; to compare the gastric acidity in rheumatoid and in osteoarthritis; and to determine the difference between the gastric acidity in arthritics and that in normal subjects.

Table 1 gives a summary of the previously published reports on gastric acidity in arthritis. In no study was the distinction made between rheumatoid and osteoarthritis. The incidence of achlorhydria found in these published reports varies from 70 per cent in Coates'[1] series to zero in that of Douthwaite.[2] These results are difficult to interpret. It must be remembered that until the publication of the work of Vanzant and his associates,[3]

Table I

Published Reports on Gastric Analysis in Arthritis

	Method	Sex	No. of Cases	Achlorhydria per cent	Hypochlorhydria per cent	Normal Acidity per cent	Hyperchlorhydria per cent
Woodwark [4]	E*	—	10	20	40	0	0
Faber [5]	E	—	65	23	—	0	0
Lottrup [6]	E	—	9	44			
Bell [7]	F†	—	13	38	23	14	23
Coates [1]	E	—	20	70	5	25	0
Venables [8]	F	—	8	—	—	50	0
Douthwaite [2]	F	—	30	0	0	90	0
Ashcroft [9]	F	—	50	large proportion		0	0
Miller and Smith [10]	F	F	170	24	7	61	8
	F	M	80	17	6	61	15
Hurst [11]	F	—	15	20	33		

* E—Ewald test meal.
† F—Fractional gastric analysis.

* Received for publication April 22, 1935.
From the Arthritis Clinic, Department of Medicine, New York Post-Graduate Medical School and Hospital.

there were no reliable figures for the incidence of achlorhydria in normal subjects at various ages. The incidence of achlorhydria is now known to increase with advancing years. Since osteoarthritis is more common in older individuals it may be seen that, if among the reported cases there happened to be an undue number of osteoarthritics, the high incidence of achlorhydria in such a series might be attributable not to arthritis but to the high average age of the patients. Probably all that can be inferred from these earlier papers is that achlorhydria is a common finding in arthritis.

Method

A group of 70 patients with chronic arthritis was studied. This group consisted of an equal number of subjects with osteoarthritis and rheumatoid arthritis. Only classical cases of each type were included. Fractional gastric analysis was performed on each patient before treatment was instituted.

The Rehfuss [12] method, somewhat modified, was employed. The tube was passed and a fasting specimen obtained. Eight ounces of "Cream of Wheat," cooked with water, were then given. After this feeding 10 c.c. of the gastric content were extracted every 15 minutes. Each specimen was titrated against tenth-normal sodium hydroxide. Töpfer's reagent was used as the indicator. Histamine was administered as a gastric stimulant in a few of the analyses. We did not think it important for the purposes of this study to use it as a routine procedure.

Results

In estimating the results of our analyses the standards of Bell [7] were followed. These are somewhat at variance with those of other writers, but seem most applicable here. The previous studies of arthritics summarized in table 1 which we are comparing with our own figures, were also based on Bell's standards. These are as follows:

1. Achlorhydria, in which free hydrochloric acid is present at no period of the analysis.

2. Hypochlorhydria, in which no fraction has contained free hydrochloric acid in excess of 10 units (0.0365 per cent hydrochloric acid).

1. Gastric Acidity in Arthritis. Table 2 gives the details of each analysis, and table 3 presents a synopsis of the results in our cases. All our cases were females. The general sex incidence in our clinic is about five females to one male. Analyzed according to the standards of Bell, we find the following results: The average age of patients with rheumatoid arthritis was 41 years, and of those with osteoarthritis, 52 years. The incidence of achlorhydria, nevertheless, was 28.6 per cent in the former group, compared with 25.7 per cent in the latter. The incidence of subacidity totalled 45.6 per cent in rheumatoid arthritis and 28.7 per cent in osteoarthritis. It is to be noted also from table 2 that the general trend toward increased acidity is greater in the osteoarthritis group.

TABLE II
Fractional Gastric Analysis in Rheumatoid and Osteoarthritis

Rheumatoid Arthritis 35 cases								Osteoarthritis 35 cases							
Number of case	Fasting	Minutes after Feeding						Number of case	Fasting	Minutes after Feeding					
		15	30	45	60	75	90			15	30	45	60	75	90
29	0*	0	0	0	0	0	0	27	0*	0	0	0	0	—	—
25	0	0	0	0	0	0	0	1	0	0	0	0	0	0	—
22	0	0	0	0	0	0	0	12	0	0	0	0	0	—	—
14	0	0	0	0	0	0	0	15	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	21	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	16	0	0	0	0	0	0	—
27	0	0	0	0	0	0	0	34	0	0	0	0	—	—	—
31	0	0	0	0	0	0	0	19	0	0	0	0	0	0	—
13	0	0	0	0	0	0	0	13	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	20	0	0	0	0	5	1	0
20	0	0	0	0	0	0	2	28	0	0	0	13	9	9	20
34	0	0	9	0	0	0	0	22	0	0	7	12	15	—	—
1	0	0	2	1	1	0	0	3	0	0	20	17	9	1	0
8	0	0	0	4	0	—	—	7	0	0	0	0	0	26	28
10	0	8	10	0	0	0	3	18	0	0	0	0	29	14	17
26	0	0	5	10	8	0	0	25	0	0	16	21	11	10	8
30	0	0	0	0	0	13	0	14	0	0	16	34	36	42	48
24	0	0	5	14	18	—	—	26	0	15	16	60	26	16	36
17	0	0	2	8	21	0	—	11	0	15	40	24	23	25	10
16	0	0	3	—	26	30	28	4	0	0	19	44	25	28	—
32	0	0	10	18	2	3	0	17	0	15	20	30	40	—	—
33	0	0	2	4	24	10	11	24	0	16	28	45	50	57	68
12	0	10	20	24	—	—	—	31	0	0	21	37	30	42	31
3	0	0	0	14	15	0	0	30	0	22	27	16	0	18	0
21	0	0	13	25	11	0	0	29	0	22	10	58	56	63	56
7	0	0	10	31	34	28	0	8	13	23	36	29	15	30	—
18	0	1	18	20	15	—	—	32	15	48	58	51	34	33	30
2	0	0	20	17	9	1	—	10	0	36	45	33	30	42	42
19	0	10	30	33	—	15	25	6	20	41	46	54	38	13	0
11	0	24	20	42	22	27	24	33	24	22	20	29	39	38	48
23	0	5	40	40	42	50	20	2	7	47	55	76	78	85	—
28	0	21	45	45	18	—	—	5	22	53	54	66	87	85	92
9	28	30	52	34	—	—	—	23	30	30	35	20	5	5	25
5	0	10	24	36	43	60	43	9	38	17	33	30	41	50	23
4	13	18	26	83	65	52	15	35	72	18	16	20	13	47	—

* HCl in terms of tenth normal sodium hydroxide.

TABLE III
Summary of Results in Rheumatoid and Osteoarthritis

	Sex		Average age	Achlorhydria	Hypochlorhydria
	M.	F.			
Rheumatoid Arthritis (35 cases).....		100%	41 yrs.	28.6% (10 cases)	17% (6 cases)
Osteoarthritis (35 cases).....		100%	52 yrs.	25.7% (9 cases)	3% (1 case)

2. Comparison of Gastric Acidity in Arthritics with That in Normal Subjects. It is now generally accepted that achlorhydria may occur in otherwise normal people, and that there is a steady increase in the incidence of this anacidity from youth to old age. Vanzant et al.[3] of the Mayo Clinic made a study of the gastric analyses of 3,746 subjects who had been found free of any disease affecting the mucous membrane or secretory activity of the stomach. Their data on the incidence of achlorhydria in this group appear in table 4. We are quoting only that part of their work relating to "true achlorhydria," where free acid did not appear either after repeated fractional analysis or after the injection of histamine.

TABLE IV

Prevalence of True Achlorhydria *

Age in years	Males			Females		
	Cases	Per Cent	Total Cases	Cases	Per Cent	Total Cases
20–24	—	—	111	3	3.2	94
25–29	8	3.6	220	9	5.8	156
30–34	5	3.0	169	13	7.6	172
35–39	9	3.9	232	24	11.1	217
40–44	27	10.3	263	17	10.9	156
45–49	19	9.3	203	18	14.8	122
50–54	37	18.5	200	27	15.8	171
55–59	27	17.8	152	31	20.8	149
60–64	36	23.1	156	39	28.1	139
65–69	24	23.0	103	15	26.3	57
70–74	7	20.6	34	5	23.8	31
75–79	2	18.2	11			
Total	200	10.8	1,854	201	13.8	1,454

* After Vanzant et al.[3]

Most of our cases of rheumatoid arthritis range between 30 and 50 years of age, the average being 41 years. In Vanzant's group of normal females between these ages the average incidence of achlorhydria was 10.8 per cent. This figure is much lower than the 28.6 per cent which we found in our series of rheumatoid arthritis. Our group of osteoarthritis patients varied between 40 and 60, the average being 52 years. In Vanzant's normals of this age, the incidence of achlorhydria was 15.5 per cent, whereas in our osteoarthritics the incidence was 25.7 per cent.

In figures most comparable to Vanzant's, published by Sagal, Marks, and Kantor,[13] summarizing the findings of gastric acid in 6,679 ambulatory gastrointestinal cases, we find that the incidence of achlorhydria from 30 to 50 years is 6.5 per cent, and from 40 to 60, 12 per cent.

DISCUSSION

The status of gastric acidity in arthritis is important for a proper appreciation of the disease as a whole. Although in the past opinions have

been held to the contrary, it is now generally accepted that achlorhydria, when found in arthritis, is a secondary factor and probably not directly related to the basic etiology of the disease. It is probably an attribute of the constitutional inadequacy so prominent in arthritis. Other conditions characterized by general debility are known to be associated with increased incidence of anacidity. In addition to the well-known variations of gastric acidity in gastrointestinal conditions, free hydrochloric acid is known to be absent or diminished at times in acute infectious diseases such as typhoid and paratyphoid, and after such acute infections as typhus, influenza, pneumonia, and enteritis. In malaria and pulmonary tuberculosis it has been noted that achlorhydria and hypochlorhydria become more common as the disease progresses. In addition to its presence in pernicious anemia where it may have a causal relationship to the etiology, achlorhydria has been found frequently in other chronic, debilitating diseases such as diabetes mellitus, hyperthyroidism, and pellagra.

It has been pointed out that high carbohydrate intake tends to lower gastric acidity. Large amounts of cane sugar (100 grams) or glucose in concentrated solution markedly depress gastric secretion and delay evacuation of the stomach. The high carbohydrate intake of pre-arthritis patients has received comment in the literature.

The rôle of the sympathetic nervous system in gastric secretion is probably important, and its function is known to be deranged in rheumatoid arthritis. Cannon [14] states that in normal men and animals all painful stimuli cause some inhibition of the entire phase of gastric secretion, as do fear, anger, anxiety, and kindred emotions. For this reason, the continuous or sudden pain associated with arthritis may be an etiological factor in these gastric findings.

There still exists a dispute as to the mechanism of achlorhydria. The older idea was that achlorhydria is usually due to a gastritis of the chronic type and that the infection, possibly introduced with food, is generally blood-borne and secondary to disease in some other part of the body. More recently, it has been held that there is more evidence favoring the belief that it is a congenital condition. There may be a familial tendency.

The exact effect of achlorhydria on gastrointestinal function is not clear. Its responsibility as a cause of diarrhea is minimized today. Heath, Castle, and Strauss [15] have shown that the intrinsic factor is not absent in achlorhydria except in the presence of pernicious anemia. It has been stated that a lack of acid in the stomach allows swallowed bacteria to enter the intestinal tract. Recent work of Furby and Arnold,[16] however, throws doubt on the bactericidal powers of free hydrochloric acid in relation to stomach and intestinal bacteria.

Our studies lead us to believe that achlorhydria occurs frequently enough to be an important part of the clinical picture in chronic arthritis. In this condition the administration of hydrochloric acid appears to be of benefit when indicated by diminished gastric acidity.

Conclusions

1. In a group of 70 patients with chronic arthritis, achlorhydria occurred in 28.6 per cent of the cases with rheumatoid arthritis, and in 25.6 per cent of the cases with osteoarthritis; hypochlorhydria was detected in 17 per cent of the former and in 3 per cent of the latter.

2. The incidence of subacidity was greater in rheumatoid arthritis than in osteoarthritis, although the latter represented an older age group.

3. Achlorhydria and hypochlorhydria appeared with remarkably greater frequency in our group of arthritic patients than in normal subjects of the same age.

4. Subacidity appears with such frequency in chronic arthritis that it must be considered an important feature of the clinical picture of that disease.

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DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE LIVER*

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An adequate discussion of the differential diagnosis of liver disease would have to consider the following groups:

1. Hepatitis, toxic and infectious.
2. Hepatocholangitis.
3. Hepatic-intestinal toxemia.
4. Simple hepatic cirrhosis.
5. Pigmented cirrhosis with anthracosis.
6. Cirrhosis with hemochromatosis.
7. Kinnear-Wilson cirrhosis.
8. So-called Banti's disease.
9. So-called Tropical Liver.
10. Cancer of the liver.
11. Syphilis of the liver (relatively common).
12. Tuberculosis of the liver (comparatively rare).
13. Hydatid cysts (dog disease) and other cysts.
14. Distomiasis or liver fluke (sheep or fish disease).
15. Trematode or other parasitic disease.
16. Amebic abscess.
17. Various bacterial abscesses.
18. Acute fatty degeneration (chloroform, phosphorus, carbon tetrachloride, etc.).
19. Acute yellow atrophy or acute necrosis (various arsenicals: atophan, cinchophen, farastan, etc.).
20. Acute ictero-hemorrhagic spirochetosis (Weil's disease).
21. Hemolytic jaundice with splenomegaly.
22. So-called simple catarrhal jaundice.
23. Various liver conditions in relation to gall-bladder disease.

It is obviously not feasible to cover this ground in a brief paper and therefore only three groups of cases will be discussed: the toxemias, the cirrhoses and acute yellow atrophy.

I feel it is fair to assume that in biliary tract disease as in other system diseases, disturbances of function precede the development of structural changes. Therefore, it is most important to learn to recognize some of the early signs and symptoms of functional liver disease, and to know the pathways by which the toxic effects created thereby may reach the liver and other vital organs of the body by vicious circle routes, thus preparing the way for organic disease.

In advanced liver disease the differential diagnosis is relatively easy. The history and physical examination coupled with good clinical experience may often alone suggest or actually make the broad major diagnosis. But in early states, and indeed in later stages, of liver disease there is so often a

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merging or overlapping of changes in hepato-cellular structure or hepatic damage that one derives much assistance from the laboratory and from duodenal tube studies and from roentgen-ray observations in clarifying the details. Tests for liver function enable us, at least to some extent, to classify better the type of liver disease with which we are dealing.

It is highly important that we learn to recognize the early cirrhosis case by symptoms, signs and laboratory studies before the classical picture has developed and decompensation has occurred. It is certainly no greater diagnostic feat to recognize the terminal picture of either portal or biliary cirrhosis than to recognize the terminal picture of decompensated renal disease as described by Richard Bright over a hundred years ago. The nephritic with marked anemia, edema or general anasarca, cardiac malfunction with chronic passive congestion of liver and other organs, a urine boiling solid with albumin and loaded with granular and waxy casts presents a striking clinical picture. The case with advanced decompensated cirrhosis is likewise easily recognized by his hepatic facies, his pinched sunken features, his sallow color or actual jaundice; his emaciated costal cage, his broom stick arms, his usually greatly enlarged abdomen, distended by ascites; his spindle legs, or in later stages with cardiorenal decompensation, his ankle, leg and scrotal edema; his distended abdominal collateral veins, perhaps a true *caput medusae;* his hemorrhoids and frequently his esophageal varices; his enlarged or shrunken liver. Such marked physical signs constitute an easily identified picture, but this picture is a terminal one.

The time to recognize and to treat cirrhosis of the liver is in the early or latent or compensated stage so that the terminal decompensated stage with ascites may be prevented or become less frequent. I now have a number of such cases recognized clinically and proved by biopsy at exploratory laparotomy, whose disease has been controlled for 10 to 15 years and for whom paracentesis, the ammonia salts and the mercurials, novasurol and salyrgan have not been required. All patients with potential or early known liver disease should select a diet high in carbohydrates, drink no alcohol, guard against a thyrotoxicosis, and against respiratory and enteric disease, and lead an outdoor life. In addition, courses of biliary drainage of the liver for detoxifying purposes and a safe biliary secretogogue, such as decholin should be used. They should be particularly warned against the use of the arsenicals (arsphenamine, neoarsphenamine, even cacodylate of soda) and the quinoline derivatives (atophan, cinchophen, farastan and the like). If such a patient has to undergo operation chloroform as an anesthetic should never be used.

The early symptoms and signs of potential cirrhosis of the liver are similar to those which also occur in the hepatic-intestinal toxemias and in mild hepatitis (the latter less common in America than in tropical zones, where it eventuates in the so-called tropical liver). In all of these conditions there may be an antecedent history of simple catarrhal jaundice, of typhoid or other enteric fever, of constipation from childhood up; perhaps

a statement that calomel courses, or saline purges have been used for years, finally creating and completing the constipation-laxative-enema habit vicious circle. Perhaps an antecedent history may be obtained of the use of the arsenicals, the quinolines, of excess iron or copper, or of a preceding chloroform anesthesia.

These are factors which prepare the way for subsequent structural change. In my opinion the two most important, and perhaps least studied, functions of the liver are its detoxifying power, for instance its ability to deaminize the poisonous amino acids, and its bacteriolytic or bactericidal power, that is its ability to entirely destroy or at least kill the bacteria brought to the liver by the blood, especially the mesenteric-splenic-portal blood.

In the early stages of a potential cirrhosis the patient complains of undue fatigability, a sense of torpor or lethargy. He is unrefreshed after more than eight hours' sleep, which may be heavy but is often broken by disturbed dream states, or even by severe nightmares. Frequently—if one questions—mild to severe cramps in toe, foot arch or leg muscles will be complained of. Diurnal drowsiness, particularly after meals, is common. Patients say that they feel "toxic" or doped. They lose alertness, state that they cannot concentrate, that they feel mentally confused and are increasingly forgetful. Some speak of momentary dizziness, of dancing scotomata or *muscae volitantes;* and some give a history of biliary migraine and vomiting. They may be emotional or tearful; or they may be pessimistic, gloomy, depressed, or even may develop severe melancholia. They are petulant over their appearance, complaining of their sallow color and frequently of acne vulgaris. One will note that the blonds become increasingly sallow, the brunettes increasingly swarthy. The sclerae are icteric, the stools slightly deficient in bile, the urobilinogen index is high, indican may be in excess; liver spots or cloasmata may appear, sometimes petechiae or "ruby points" may come and go. Telangiectases, even the small spider web type, above the costal margins are important signs to note. The differential values of the Van den Bergh test are often helpful. The icterus index may show latent if not actual jaundice. There may be an increase in uric acid, undestroyed by the liver; a diminution of urea, insufficiently formed by the liver; possibly an increase of blood cholesterol. These are all helpful when present but are frequently absent. Bromsulphalein retention, when present, and evidence of diminished liver secretion and excretion of bile as determined by duodenal tube study are of diagnostic value. A positive galactose test suggests hepato-cellular damage but is usually negative in the early stage with which we are now concerned.

It is a question how patients, presenting the above described clinical features, should be classified. In earlier publications, for want of better terms, I have designated them as hepatic toxemias, intestinal toxemias and, when overlapping symptoms were present, as hepatic-intestinal toxemias.

Certainly such symptoms and signs are often the prelude to the appear-

ance of more striking clinical pictures of toxemia or hepatitis, or of cirrhosis itself. The part played in the later evolution of the disease by such factors as disease of the gall-bladder, the heart, the pancreas or the colon must be passed over in this brief summary as must also the existence and importance of certain vicious circles which I have described elsewhere.[1]

Now let us turn to a very brief discussion of the classification of the cirrhoses. One may follow either Chauffard's classification which outlines the methods by which cirrhosis is induced, or one of the classifications based upon purely anatomical considerations, such as Adami's or Senator's. However, I prefer Rolleston's classification with its simple division into two main groups. This seems preferable to an etiologic classification, since the causes of cirrhosis are legion; or to a classification based on size, hypertrophic and atrophic; or to an attempt to classify by the relative involvement of the liver and spleen, such as is implied in the terms hepatomegalic, splenomegalic or hypersplenomegalic biliary cirrhosis, etc. Rolleston's classification appeals by its simplicity and by its quick approach to the more common clinical features. He divides the cirrhoses into

1. *Ordinary or common cirrhosis.* Elsewhere this is variously described as portal cirrhosis, Läennec's cirrhosis, multilobular cirrhosis, alcoholic cirrhosis and even chronic interstitial hepatitis. In this form, hematemesis is an early symptom; ascites a terminal incident. Jaundice is not prominent. The liver may be either large or small but is multilobularly involved. The spleen is at times enlarged but not so constantly as in group two.
2. *Biliary cirrhosis.* Here jaundice is prominent and long continued. Hematemesis and ascites are both less common, although ascites in small amounts may occur just before death. The liver is always enlarged, often extremely so, reaching a weight of 4500 to 6000 grams. The surface is smooth and unilobular. The spleen is usually enlarged, often greatly so. This group Rolleston subdivides into (*a*) a simple hypertrophic biliary cirrhosis, and (*b*) obstructive biliary cirrhosis (for instance common duct gall stone).

There are further variations and enlargements of the above two main groups depending on associated lesions such as carcinoma, syphilis, malaria, various cysts, various abscesses, chronic passive congestion from a failing heart, hemolytic jaundice with splenomegaly and so on, all of which add distinctive features and signs which need not be discussed at this time. There are also rarer forms of cirrhosis which must be classed separately: the pigmented cirrhosis with anthracosis (miner's disease); cirrhosis with hemochromatosis—so-called bronzed diabetes with glycosuria; and that rare and obscure cirrhosis described by Kinnear-Wilson with neurological signs pointing to involvement of the lenticular nucleus in the brain.

I apologize for merely outlining this important subject so that there may be space to devote to a very brief word picture of acute yellow atrophy of the liver or, more properly called, acute necrosis. This is a dreadful malady. It is characterized by decreasing size of the liver, by jaundice, fever, by certain nervous symptoms and too frequently by a fatal termina-

tion. Some cases called subacute yellow atrophy differ only by the degree and not by the character of the illness and may recover with appropriate treatment, as did a case we recently reported.[2] As particularly dangerous causative factors may be mentioned chloroform narcosis; phosphorus poisoning, the arsenical and quinoline derivatives; carbon tetrachloride; and exposure to the fumes of trinitrotoluene (T.N.T.) and tetrachlorethane. As in other liver diseases the ground has been prepared or the patient possesses an individual susceptibility to either the disease itself or to some agent which causes it. For instance, a fatal case which I saw recently in consultation during the third stage could be traced back to 17 tablets of cinchophen taken for "arthritis." The arthritis may have helped to prepare the ground and the patient's idiosyncrasy to cinchophen did the rest.

The onset is usually insidious because of a latent period of two to four weeks. Indefinite malaise; early, mild digestive symptoms or a jaundice at first undistinguished from the simple catarrhal variety may be the initial symptoms. There may be vomiting, muscular pains, constipation with bile deficient stools, and bilirubinuria. These features characterize the first stage.

The onset of the second stage is a turn for the worse with the appearance of nervous symptoms. Headache becomes more intense, photophobia, dullness, restlessness and delirium. Muscular twitchings extend from isolated muscle groups into general convulsions. Babinski's sign is present. If one excepts the jaundice the clinical picture resembles meningitis.

In the third stage vomiting becomes more troublesome, and may be bloody; the pupils dilate, the pulse is rapid and thready; respirations increase; the temperature may be subnormal or rapidly rise to high fever levels; frequently petechiae and submucous hemorrhages occur; drowsiness becomes progressive; the patient lapses into coma and usually dies.

The liver may at first be swollen but rather quickly shrinks and shrinks so that but little percussion dullness may remain. The jaundice may increase but never becomes of the obstructive type, the urobilinogen index rising to higher levels. The stools are light colored but not clay white. The urine appears like strong tea. The blood coagulates slowly and contains excess bilirubin; its cholesterol content may vary but is usually decreased; amino acids, leucine and tyrosine, are in excess both in the blood and urine. Urea is diminished; uric acid is increased. Positive blood cultures are rare, even for *B. coli.* Blood sugar decreases to dangerously low levels and this decrease parallels the clinical severity of the disease. Bromsulphalein dye is retained in the blood. The Van den Bergh test yields a biphasic or a delayed direct reaction. The galactose test may be positive up to a urine content of six or more grams.

Aside from the above details the diagnosis can be suspected because of the jaundice with severe constitutional and cerebral symptoms and particularly because of the decreasing size of the liver.

All patients should be given the benefit of urgent treatment, since some

recover, and more will do so by proper treatment. This consists of warmth to liver region, blood transfusions, intravenous sugar, carbohydrate fluids by mouth, salt and sugar by bowel and subcutaneously, duodenal drainage to remove toxins and general supportive measures. Bile salt preparations by mouth or vein are dangerous until after jaundice has subsided. If one must be tried, decholin is the safest. Sometimes calcium by vein and buttocks and parathormone may help.

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TREATMENT OF PERIPHERAL VASCULAR DISEASE BY MEANS OF SUCTION AND PRESSURE *

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At the meeting of the College in 1934, one of us presented certain observations [1] indicating that blood flow to the extremities could be increased at least temporarily by applying alternate negative and positive pressure. In patients with peripheral vascular disease and advanced organic arterial occlusion this procedure elevated skin temperature conspicuously, often relieved cyanosis, usually diminished rest pain and favored the healing of indolent ulcers. While symptoms were quite generally relieved it was then felt impossible to do more than speculate upon the permanence of that improvement. To quote the statement then made, "The practical importance of suction and pressure in the treatment of peripheral vascular disease will necessarily depend to a great extent on the degree to which collateral vessels take over the function of those arteries which are closed by disease. Sufficient time has not elapsed to justify any conclusions concerning the real clinical usefulness of the procedure."

It is the purpose of the present report to present a summary of our experience in the first 75 cases subjected to suction and pressure therapy (table 1). An attempt will be made to give a fair cross-section of general

Table I

Summary of 75 Consecutive Cases Treated by Means of Suction and Pressure

Diagnosis	Number	Age—Years			Suction and Pressure Therapy—Hours		
		Average	Highest	Lowest	Average	Highest	Lowest
Arteriosclerosis, senile	23	69	80	52	22	91	2
Thromboangiitis obliterans	22	41	61	26	31	119	5
Diabetes, arteriosclerosis	30	62	78	42	26	90	2
Total	75						

Note: Treatment for two to five hours represents merely attempted palliation in patients in whom conservative therapy was essentially hopeless.

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results in hospital cases and out-patients, including, without omission, all cases so far treated even briefly by this method.

The apparatus used was the same as that described previously.[2, 3] During treatment the patients sat or reclined in bed. The affected extremity was inserted into an aluminium chamber and lay in the horizontal plane upon a pillow in the bottom of the chamber. The thigh, protected when necessary by a layer of gauze bandage, was encircled at a point approximately six inches above the knee by a rubber cuff with two leaves, one sealing during pressure, the other sealing during suction. A layer of adhesive tape was applied to each cuff to keep the rubber in close contact with the skin. Suction amounting to between 80 and 120 mm. of Hg was applied for 25 seconds alternately with positive pressure of 40 to 80 mm. of Hg for 5 seconds. The time required to change the air pressure within the aluminium chamber from — 120 to + 80 mm. of Hg was reduced to about 3 seconds in order that the negative pressure might be applied as efficiently as possible. Until patients became familiar with the apparatus it was usually expedient to use — 80 and + 60 mm. of Hg for 25 and 5 seconds, respectively, increasing to — 120 and + 80 mm. of Hg unless large changes of pressure were contraindicated.

In general when rest pain was severe, or when ulcers had not yet begun to heal, the affected extremities were exposed to suction and pressure for one or two hours twice daily. After rest pain had diminished somewhat and after ulcers had begun to heal, the duration of treatment was reduced to one or two hours at first once daily, then three times weekly and finally to one or two hours once weekly. Out-patients with relatively mild symptoms were treated for periods of one or two hours three times weekly or less.

Ulcers were dressed daily with vaseline gauze; antiseptics were used only rarely, since even the mildest seemed to delay the growth of granulation tissue and epithelium in ischemic extremities. Parts involved in dry gangrene were merely covered with sterile gauze.

A few of the patients had previously received citrate solution or typhoid vaccine intravenously without relief. Most of the ward patients had been treated by other conservative means, including particularly the thermoregulated cradle and vasodilator drugs, before suction and pressure were resorted to on account of persisting symptoms. In these cases the thermoregulated cradle was used during the intervals between suction and pressure treatments. Out-patients received the usual advice concerning care of the extremities and smoking. They were advised to use hot sitz baths and in selected instances salt solution by mouth was prescribed.

The extent of organic occlusion and the development of collateral circulation were tested at intervals by measuring skin temperature while the forearms were heated, either by means of warm water or electric pads.

The 75 cases considered in this report include 23 with arteriosclerosis, 22 with thromboangiitis obliterans and 30 with diabetes and arteriosclerosis. The average age of the arteriosclerotic group was 69 years, ranging from

80 to 52. The ages of the diabetic patients averaged 62 years, while the patients with thromboangiitis obliterans were approximately 20 years younger, averaging 41 years.

Owing to limited facilities it was possible only to assist in recovery from the more advanced manifestations of ischemia,—severe rest pain, indolent ulceration or marked intermittent claudication. No attempt could be made to continue suction and pressure therapy as a prophylactic measure in order to avoid recurrences or to avert future difficulties. The average amount of treatment ranged from 22 to 31 hours with several instances of 90 hours or more. Treatment totalling only a few hours (such as two or five hours) represents attempted palliation in patients in whom any conservative therapy was essentially hopeless from the outset. It was our purpose, however, to observe the effects of suction and pressure on peripheral vascular disease of all grades of severity, including even the most hopeless cases.

The general results are shown in table 2 in which the effects have been tabulated under the headings good, fair and poor. A good result includes

TABLE II

General Results of Suction and Pressure Therapy

Result	Number of Cases	Per Cent	
Good	38	51	64
Fair	10	13	
Poor	27	36	
Total	75		

Analysis of Cases Designated "Poor."

Too far advanced. Massive gangrene or sloughs	6	*Amputations*	10
Infection	4		
Drifted away	5		
Incomplete	12		
Total	27		

obliteration of rest pain, distinct lessening of claudication and the complete healing of ulcers previously increasing or indolent under other conservative measures. Such outstanding relief, which could in all fairness be attributed to suction and pressure therapy, was observed in 51 per cent of the 75 cases. A fair result includes almost, but not quite, complete relief of rest pain, slight but definite lessening of claudication, and healing of lesions except for very small sinuses or minute areas. There was no evidence of advance in symptoms or signs, the tendency being toward very slow improvement in this group which comprises 13 per cent of the total.

The designation "poor" has been used to indicate that the relief of symptoms ordinarily observed *immediately during* suction and pressure therapy has not been accompanied by significant relief of symptoms *between*

treatments. It is possible that prolonged and frequent therapy might accomplish more than the limited amount we have been able to use in these cases. This group includes six patients who had massive gangrene or deep sloughs, in the face of which suction and pressure therapy was useless except as a temporary palliative measure. Four patients had, or developed, advancing infection. These 10 cases required amputation eventually. Five cases listed as poor results drifted away, three of these in spite of definite improvement, two because of dissatisfaction with the results obtained. The remaining 12 patients are still under treatment which is incomplete and has not progressed far enough to permit estimation of eventual results. Six of these 12 patients, however, are showing encouraging progress at the present time.

It may be concluded that "good" and "fair" results were obtained in 64 per cent, any error being, we believe, in the direction of too low a figure. Similarly the estimate of poor results in 36 per cent is probably too high since it includes certain cases which we would now regard as hopeless from the outset, and a certain number in which therapy has not had a fair trial.

When the results of suction and pressure therapy are arranged according to diagnosis (table 3) it becomes evident that the poorest results have been

TABLE III

Results of Suction and Pressure Therapy According to Diagnosis

Diagnosis	Result			Total
	Good	Fair	Poor	
Arteriosclerosis	12	3	8	23
	52%	13%	35%	
Thromboangiitis obliterans	14	1	7	22
	64%	5%	31%	
Diabetes	12	6	12	30
	40%	20%	40%	

obtained in diabetes, with slightly better results in simple arteriosclerosis. The highest percentage of good results was obtained in thromboangiitis obliterans. This distribution agrees in general with observations on other types of conservative therapy.

Landis and Hitzrot [4] published, in March 1935, a summary of the results observed in 30 cases treated up to July 1934 (table 4). A "good or fair" result was obtained in 24 cases. Most of these patients were hospitalized and had been treated conservatively by the usual methods without success prior to the use of suction and pressure therapy. The apparent benefit derived in these 24 patients seemed therefore more significant than it would have been if unselected cases had been treated. It has been possible to obtain follow-up data on 23 of these 24 cases. Thirteen had no further symptoms of peripheral vascular disease during 6 to 22 months after discharge,

TABLE IV

Persistence of Improvement Once Obtained

Of 30 severe cases (Landis and Hitzrot,[4] treated prior to July 1934 and reported March 1935)

6 Poor
24 Good and fair

Of the 24

13—No further symptoms in 6 to 22 mos. (average 11 mos.)
1—Mild recurrence, yielding to treatment
6—Died, ages 78, 62, 57, 55, 75, 46
1—Cerebral hemorrhage
3—Pneumonia
2—Coronary occlusion
3—Relapses
2—Amputation of leg
1—Amputation of toe
1—Lost

Total 24

the average period being 11 months. One case presented a mild recurrence yielding easily to suction and pressure therapy. Six patients died, one of cerebral hemorrhage, three of pneumonia, and two of coronary occlusion. The causes of death alone indicate the precarious general condition of most patients with advanced peripheral vascular disease. Definite relapses were observed in three instances after suction and pressure therapy had healed indolent and painful lesions. In the first patient a necrotic lesion of the great toe appeared six months after discharge and advanced slowly in spite of suction and pressure therapy. Amputation of the leg above the knee revealed marked sclerosis of the femoral artery. A second case appeared four months after discharge with gangrene of a toe in which ascending infection contraindicated the use of suction and pressure, leading finally to amputation above the knee. The third case suffered from subacute thromboangiitis obliterans which had already required amputation of three digits in the course of two years. Suction and pressure had been required to heal the ulcer remaining after the last amputation. One year later the patient reappeared with a deep ulcer at the base of another digit. Involvement of an interphalangeal joint and osteomyelitis of a phalanx contraindicated suction and pressure therapy. The fifth toe was amputated in January 1935, local heat, vasodilator drugs and suction and pressure being used to aid healing of the wound. Whether or not continued treatment of these three patients after discharge from the hospital would have modified the final result is not known. These relapses suggest, however, the need for continuous after-treatment even though ulcers have healed and rest pain has disappeared.

A number of other patients not shown in this table have been followed over briefer periods of time after suction and pressure therapy has been stopped. If these are included, the follow-up data indicate continued relief in at least 26 patients of the group from one month to two years after discontinuance of suction and pressure therapy.

An analysis of possible causes of relapse in 6 of the 48 cases discharged with good or fair result is of considerable interest (table 5). Discharge from the hospital with an imperfectly drained lesion was followed by a

TABLE V

Causes of Relapse—6 Cases in 48 with Fair or Good Result

A. Discharged with imperfectly drained lesion 1
   2 mos.—healed with renewed treatment.
B. Advancing subacute thromboangiitis obliterans 2
   (*a*) 1 year—gangrene of toe, amputation of toe.
   (*b*) 6 weeks—return of rest pain.
C. Widespread advanced arteriosclerosis 3
   (*a*) 6 mos.—ulcer healed with renewed treatment.
   (*b*) 4 mos.—gangrene toe, mid-thigh amputation, sclerosed femoral artery.
   (*c*) 6 mos.—gangrene toe and infection, mid-thigh amputation.

relapse with increased rest pain and increased ulceration at the end of two months. This ulcer was healed with difficulty by renewed treatment. In acute or subacute thromboangiitis, recurrence or relapses can be expected since the disease ordinarily advances at a rate too rapid to allow the compensatory development of collateral blood flow. One patient returned in a year with gangrene of a toe requiring amputation. Another with severe rest pain returned after six weeks with renewed rest pain, the first period of treatment having been quite definitely insufficient.

Widespread advanced arteriosclerosis involving the femoral artery seemed to be responsible for at least three recurrences at four to six months after cessation of treatment. In one patient renewed treatment was successful in healing the lesion. In two patients previously mentioned, mid-thigh amputation was necessary, one on account of advancing gangrene and the other on account of acute infection.

As might be expected from the advanced age of at least two-thirds of these patients the death rate in a group followed over two and a half years is relatively high (table 6). Eleven of the 75 cases treated with suction and pressure therapy have died, three of coronary occlusion, one of cerebral hemorrhage, four after amputation and three from pneumonia. The lower

TABLE VI

Deaths—11 of 75 Cases

1. Coronary occlusion 3
2. Cerebral hemorrhage after prostatic punch operation 1
3. Post-amputation 4
4. Pneumonia 3

Possible Injurious Effects of Suction and Pressure Therapy

1. Amputation hurried 3
   In 2 amputation inevitable before suction-pressure therapy.
   In 1 amputation being seriously considered.
   In all 3 suction-pressure therapy used to exhaust all possible conservative measures.
2. Thrombosis or embolus ..... none
3. Petechiae 2
   Both diabetics, no sequelae.

portion of the table presents possible injurious effects of suction and pressure therapy. In two of these cases amputation was inevitable before suction and pressure were applied, the procedure being tried only to exhaust the use of all possible conservative measures. In the third case amputation was hastened owing to the development of ascending infection. In this instance amputation was being seriously considered as the only alternative before suction and pressure therapy was started as a last resort. We have observed no instances of massive thrombosis or embolism. A few cases have become progressively worse during suction and pressure therapy, owing to the presence of massive gangrene or deeply penetrating sloughs. Though the area of gangrene slowly increased in size there was no massive increase in ischemia, and there were no symptoms or signs that could be ascribed to a large thrombus or embolus. Petechiae appeared in two diabetics with delicate skin without sequelae in either instance. Improper adjustment of the cuff above the thigh makes hemorrhages more likely to appear since constriction prevents complete evacuation of blood during the period of pressure. This complication can be avoided by adjusting the cuff carefully and by observing the emptying of the vessels during pressure.

TABLE VII

Factors Predisposing to Failure or Very Slow Improvement in 12 Cases: ("Poor Result")

Extreme arterial occlusion	8
Massive gangrene or slough	8
Badly infected lesions	5
Osteomyelitis	3
Severe dermatophytosis	2

It is essential to know what conditions are most apt to lead to failure of conservative therapy including suction and pressure (table 7). In 12 cases classified under "poor results" suction and pressure therapy, after fair trial, failed to arrest the effects of ischemia. Extreme arterial occlusion involving the large vessels was present in eight cases. Deeply extending gangrene or massive sloughs were present in eight cases. In these patients the immediate problem is primarily mechanical since devitalized tissue must be removed before healing can take place. Infection and pain are both apt to increase as long as necrotic tissue remains. Judicious surgery plus suction and pressure therapy should yield better results than either procedure alone.

Infection appeared to be extending in five cases. Acute ulcers are more dangerous to treat by suction and pressure than are chronic ulcers which are well walled off by inflammatory tissue. While patients with open lesions are being treated it is essential to investigate the extremity before each treatment in order to be certain that there is no phlebitis and that infection is not spreading. Patients with even slight elevation of temperature should be treated only with the utmost caution. If the presence of encapsulated pus is suspected suction and pressure therapy should not be used. When

such lesions are present external drainage must be complete and continuous. It is this possibility of harm from spreading infection that makes suction and pressure therapy distinctly not a routine procedure. On the contrary, it can be decidedly dangerous under some circumstances. Patients who are undergoing suction and pressure therapy must be followed carefully by a physician,—they cannot be left to the attention of technicians alone.

Osteomyelitis was present in three cases. As might be expected cutaneous lesions healed satisfactorily, but as long as drainage from the infected bone continued sinuses remained. These sinuses could not be closed by suction and pressure therapy. Osteomyelitis was responsible for one amputation after a cutaneous lesion had disappeared; and was responsible for two "fair" results in which sinuses remained after the cutaneous lesions and the symptoms had largely disappeared. Severe dermatophytosis in conjunction with advanced organic occlusion was, we believe, responsible for two failures. It is our impression that the application of potassium permanganate even in weak solution may affect the ischemic skin deleteriously. Dermatophytosis in conjunction with very mild organic occlusion is of little consequence, but when combined with severe organic occlusion it becomes a major complication.

Fourteen cases have been studied with respect to the change in skin temperature of the lower extremities when the forearms were heated either by immersion in warm water [5] or by electric pads. In seven (table 8) of these

TABLE VIII

Increase in Vasodilator Response Following Suction and Pressure Therapy

Patient	Diagnosis	Treatment Hours	Vasodilator Response		Time Elapsed	Therapeutic Result
			Before	After		
			°C.	°C.		
1. Po.	T. A. O.	71	None	29.2	22 mos.	Good
2. He.	T. A. O.	24	None	30.2	19 mos.	Good
3. Ro.	T. A. O.	112	27.6	30.6	22 mos.	Fair (claud.)
4. Ca.	T. A. O.	20	28.0	29.5	6 mos.	Fair (osteo.)
5. Ha.	Arterioscl.	91	None	26.3	11 mos.	Good (sl. pain)
6. Li.	Diabetes	70	None	29.5	6 mos.	Good
7. Fi.	Arterioscl.	16	None	27.4	2 mos.	Good

14 cases a "good" or "fair" therapeutic result has been accompanied by definite objective evidence of improvement in collateral blood flow as measured by increase in vasodilator response. Over a period of 19 to 22 months the vasodilator response may improve remarkably, indicating that it is well worth while to temporize in crises of pain or claudication in order that time may be gained for the development of adequate collateral circulation. As this table shows, improvement in circulation may be very conspicuous by objective test.

An equally large number of patients (table 9), however, showed no measurable change in their vasodilator response after periods of two months to one year. These patients have, however, been followed over briefer periods of time and objective signs of collateral circulation may eventually develop. The relief of symptoms in this group was, in general, not as good

TABLE IX

No Change in Vasodilator Response Following Suction and Pressure Therapy

Patient	Diagnosis	Treatment Hours	Vasodilator Response		Time Elapsed	Therapeutic Result
			Before	After		
			°C.	°C.		
8. Sa.....	Arterioscl.	14	23.4	24.4	3 mos.	Moderate relief claud.
9. Ba.....	Arterioscl.	20	26.8	23.4	2 mos.	Rest pain abolished. Claud. delayed
10. Fi.....	Arterioscl.	14	29.5	29.5	2 mos.	Rest pain moderately relieved. Claud. unchanged
11. Ec.....	Arterioscl.	17	None	None	2 mos.	Ulcer healed, rest pain relieved
12. Ra.....	T. A. O.	22	None	None	2 mos.	Rest pain diminished 75%
13. Dr.....	T. A. O.	60	None	None	1 yr.	Rest pain partly relieved, ulcer healed
14. Tr.....	Diabetes	44	None	None	6 mos.	Relapse, gangrene, amputation

as in the other group who showed conspicuous increase in vasodilator response. One patient returned after six months with a relapse requiring amputation. Conservative therapy was justified, however, because of the symptomatic relief afforded each patient at least temporarily.

In summary, suction and pressure therapy has been used in the treatment of 75 patients with peripheral vascular disease. Negative pressures between — 80 and — 120 mm. Hg and positive pressures between + 40 and + 80 mm. Hg were applied alternately for 25 and 5 seconds, respectively, beginning usually with the lower pressures. Patients were treated for one to two hours at first once or twice daily, then three times weekly and finally, as the symptoms and signs diminished, once weekly.

Cyanosis was usually diminished; symptomatic improvement was sometimes observed, however, without significant change in skin color. The rest pain of ischemia was usually abolished during actual use of suction and pressure and gradually became less severe in the intervals between exposure to pressure variations. Ulcers enlarging or indolent under ordinary conservative treatment usually began to heal soon after suction and pressure therapy was instituted. Intermittent claudication became in general milder and exercise tolerance was slightly, but definitely, increased.

Suction and pressure therapy was of no definite lasting service in patients with osteomyelitis, deeply extending gangrene or large sloughs. A

certain number of patients with severe, widely disseminated arteriosclerosis did not improve.

This form of therapy is *contraindicated* in patients with phlebitis, encapsulated pus or acute spreading infection. Patients must be followed day by day so that any change in the clinical picture may be detected. It is only in this way that the possible injurious effects of suction and pressure can be avoided. The therapy should be applied with caution in appropriate cases, under the direct supervision of a physician.

Suction and pressure therapy appears to be a worth while addition to the other conservative methods of treating peripheral vascular disease. Good results can be obtained even when organic obstruction has advanced to the stage in which arterial blood flow can no longer be increased by measures depending on vasodilatation. Symptoms and signs of ischemia have been relieved when other conservative measures proved ineffectual. The method may be of particular service in increasing local blood flow temporarily during episodes of pain or ulceration, so that time is gained for the development of adequate collateral circulation. This development of collateral circulation is slow, but over periods of six to 22 months has been observed to be capable of increasing the vasodilator response in the lower extremities with persisting symptomatic improvement.

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VON GIERKE'S GLYCOGEN DISEASE *

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Since 1929, when von Gierke first reported two cases of the syndrome which now bears his name, a great interest has been shown in this disturbance of glycogen metabolism. Now that attention has been called to the disorder numerous cases have been reported from Europe, Australia and America; and a search into medical literature reveals the fact that several undoubted cases were reported under various names prior to 1929.

The disease may be defined as a disturbance of glycogen metabolism which appears in early infancy and is characterized by an abnormal deposit of glycogen in the liver, kidneys, heart and other organs which become so engorged with glycogen that they assume an enormous size. The peculiarity of this stored glycogen is that it becomes in some way fixed and cannot be mobilized to any extent by natural means.

The most striking cases are those in which the liver is chiefly involved. The infant's abdomen is noticed to be unduly large and palpation reveals the fact that the enlargement is due to the enormous size of the liver. There are no other symptoms of disturbed liver function, such as jaundice or ascites, and the Van den Bergh test is negative. The spleen is not enlarged.

The second characteristic of the disease and one dependent on the fixation of glycogen in the liver, is a permanently low blood sugar which may fall to 20 or 30 mg. per cent in the fasting state and yet not be accompanied by any symptom of the hypoglycemic syndrome. The sugar tolerance curve is abnormal being slower to rise and more prolonged than normal. Acetonuria may be present especially in the fasting state. The injection of adrenalin fails to produce the usual marked rise in blood sugar but the ketosis may be increased. Some cases show a lipemia and an abnormally high concentration of cholesterol. As might be expected the reaction to insulin is usually severe and accompanied by symptoms of shock.

The etiology of this disease is quite obscure. As regards the pathogenesis little is known. Attention has naturally been concentrated on the factors which govern glycogenesis and glycogenolysis. Normally the liver extracts glucose and other nutrients from the blood and stores them as glycogen. When the blood sugar falls below a certain level a demand is made on the liver for a supply of glucose.

The muscles also participate in the formation of glycogen from glucose. When the muscle contracts glycogen breaks down and lactic acid is formed. The latter is carried by the blood to the liver and there converted into glycogen again.

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935.

The exact mechanism by which glycogen is mobilized is not known. It appears to depend on a combination of endocrine and nervous factors. The prime governor of carbohydrate metabolism is probably insulin which not only regulates the formation of glycogen but also the combustion of glucose with resultant reduction of blood sugar. Adrenalin, on the other hand, has the faculty of mobilizing glycogen and causing a sharp rise in blood sugar and blood lactic acid. A similar rise can be produced by stimulation of the splanchnic nerves. Adrenalin probably acts on the glycogen through the medium of the enzyme, amylase, which normally controls the glucose-glycogen balance.

The secretion of the pituitary and thyroid glands is also concerned in the complex mechanism of glycogen metabolism.

In the case of von Gierke's disease the study of amylase in the liver, blood and urine by various observers has not led to uniform results. It would seem that although sufficient amylase is present in the liver and blood it cannot, for some unknown reason, liberate glucose from the glycogen. How glycogen and amylase can be found in the liver without the production of glycogenolysis is a puzzle for which various theoretical solutions have been advanced. An interesting fact which may have some bearing on the question has been observed in postmortem examination. The liver glycogen fails to disappear within a few hours after death, as should normally occur, but may be found for many days afterwards.

One must conclude that either the glycogen is of a different quality, resistant to the action of normal enzymes—or that there is some barrier between the enzymes and the glycogen. At present there is little evidence to support either of these suppositions.

Bichoff, and Putschar [1] were the first to report examples of the *cardiomegalic* form of the disease. The heart in these cases may be five or six times the normal size. The true nature of these cases has rarely been recognized before death. They have usually been considered as cases of idiopathic cardiac hypertrophy or of diffuse rhabdomyomas. The latter have been known for some time to be rich in glycogen.

The symptoms of the cardiac cases are not characteristic. The infant fails to grow and develop normally and is subject to respiratory infections. Occasionally dyspnea, cyanosis and cardiac murmurs are observed. In both cardiac and hepatic forms of the disease the surprising thing is that the function of the affected organ is apparently so little impaired.

It may be only by examining a biopsy section of the liver that the real nature of the condition can be ascertained, indeed, until recently, most cases of von Gierke's disease have been diagnosed only by postmortem examination. By proper staining it is then found that the parenchymal cells of the affected organ are greatly swollen and are engorged with large granules of glycogen.

The disease appears to be familial: several instances of two or three affected members of a family have been reported. The enlarged liver and

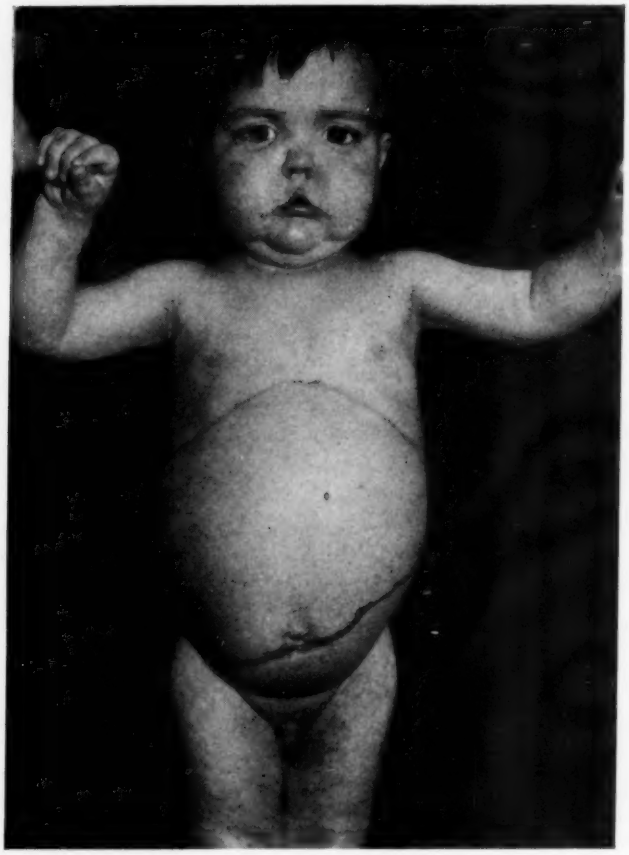


FIG. 1. Von Gierke's disease: Paul B., aged 2½ years, showing fat cheeks, large abdomen and the lower level of the liver.

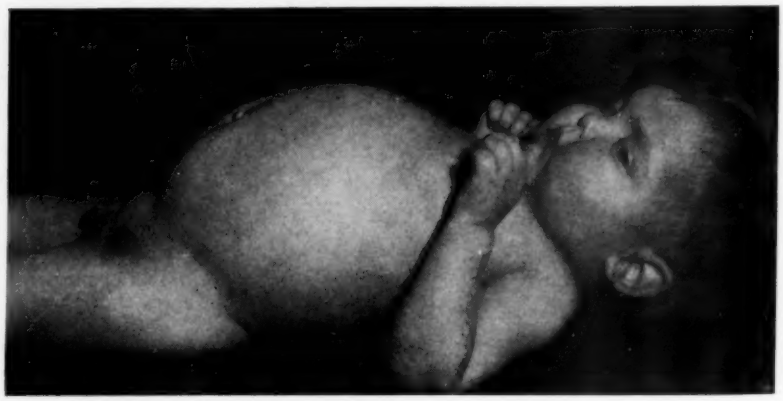


FIG. 2. Contour of body with patient in dorsal decubitus.

abdomen are noticed early in infancy and seem to progress to a certain point where they remain stationary for some years. There is evidence that those who survive to adolescence show some improvement. Physical growth is impeded and the term hepatic infantilism has been applied to certain cases.

No known treatment in any way influences the course of the disease. Many cases have died of pneumonia or other intercurrent infections. One case developed diabetes mellitus, a fact which may be of some significance. When one realizes that the nature of the disease has been recognized only for the past six years it is not surprising that so little is known of its ultimate outcome. One may expect that with continued study of suitable cases a more complete understanding not only of this disease but also of the physiology of carbohydrate metabolism will ensue.

The recent studies of van Creveld [2] in Amsterdam and Rauh and Zelson [3] in New York have added much to our knowledge of this disorder. The pathological study recently published by Humphreys and Kato [4] has also helped to clarify some of the obscure points. These observers have reviewed all cases in the literature and have added three more in which the heart was predominantly involved. They claim that there are but 15 proved cases of glycogen storage disease on record.

The following case illustrates well the hepatic type of von Gierke's disease.

Case Report

Paul B., a French Canadian boy of 27 months, was admitted to the Childrens Memorial Hospital in April 1934. His complaints were enlarged abdomen, and discharging ears.

He was the fifth child in the family; apparently a normal, full term infant weighing 7½ lbs. at birth. He was breast fed for five months and was then given a mixed diet with cod liver oil and orange juice. At seven months of age he began to vomit and his abdomen was noticed to be unduly large.

From that time until admitted to the hospital, he had frequent attacks of vomiting and his abdomen continued to enlarge slowly. His appetite was good and the bowels were regular. Three months prior to admission, he was taken acutely ill with fever and convulsions. Soon after both ears began to discharge.

His father and mother were both 36 years of age and apparently healthy. There were five other children, one of whom, a boy, had died of pneumonia at 10 months of age and this child is said to have had a "big stomach like Paul."

Examination on admission showed a rather short boy (figures 1 and 2) giving the impression of being very fat,—because of his fat cheeks and chin, and very large abdomen. There were "pads of fat" over both knees and elbows and also over the distal and middle phalanges of all fingers. In contrast to these evidences of obesity the nutrition of the arms and especially of the legs was poor and the muscles were soft and flabby. His height was 31 inches and his weight 29 lbs. There were no signs of rickets and he had 16 teeth. The skin was pale but not jaundiced. Mentally the patient was very placid and coöperative.

The lungs were negative. Auscultation of the heart revealed a systolic murmur at the apex. The radiogram showed no enlargement, though the heart was pushed up by the enlarged liver.

The abdomen was very large with dilated superficial veins over the upper part. On palpation the liver was found to be enormously large, extending below the umbilicus in the mid-line. Its surface was smooth and firm. The spleen was not palpable. There was no evidence of free fluid in the peritoneal cavity. The genitalia were normal.

Examination of the urine was negative. The Mantoux and Wassermann tests were both negative. The blood showed a mild anemia with a leukocyte count of 11,000.

Rather extensive chemical studies of the blood were made, but only the following abnormalities were found: Hypoglycemia, ranging from 20 to 37 mg. per cent, in the fasting state; low sugar tolerance curves; no rise in blood lactic acid after injection of adrenalin, but development of slight acetonuria; lipemia (0.75 per cent fatty acids) and high cholesterol, 375 mg. per cent. Tests with sugars for liver function gave normal figures.

An attempt was made to outline the kidneys by means of uroselectan, but owing to interference from the enlarged liver, satisfactory outlines indicating enlargement were not obtained.

From these clinical and biochemical observations it seemed justifiable to make the diagnosis of von Gierke's glycogen disease of the hepatic type. To corroborate the diagnosis a small section was removed from the liver. Chemical analysis of this revealed three times the normal amount of glycogen and only one-third the amount of fat usually found.

Microscopic sections (figures 3 and 4) stained by the routine (hemalum, erythrosin and saffron) method presented a very characteristic appearance. The liver cells were greatly swollen and instead of taking the cytoplasmic stain, they were tinted a faint yellow by the collagen stain (saffron). This material gives a positive reaction for glycogen both by the Best's carmine and the iodine method. The nuclei appeared normal and were centrally or excentrically situated.

The lumen of the liver sinusoids appeared to be occluded by the pressure of the enlarged parenchymal cells. A few dense elongated nuclei were the only evidence of their presence and as a result the lobules appear bloodless. Under very low power the liver presented a well lobulated appearance obviously due to an early cirrhosis of the portal type. Higher magnification showed a mild lymphocytic and polymorphonuclear infiltration of the portal spaces. Here and there could be seen one or two glycogen-laden liver cells cut off from the rest of the lobule by fibrosis.

This increase of fibrous tissue has been noted by others in connection with glycogen disease. In the light of our present knowledge our pathologist reëxamined the liver of a case of portal cirrhosis in an infant who had died 9 months previously and he found the typically enlarged liver cells filled with glycogen. From this it would seem that whatever may be the cause of glycogen disease, it tends to produce cirrhotic changes in the liver.

Now after observing the boy for just a year, we find very little change in his condition. The liver is possibly a little larger. The blood sugar curve is essentially the same. He has apparently grown only one-half inch in height and his weight is still about 30 lbs. He eats and sleeps well, feeds himself in a most deliberate fashion and has a definite penchant for potatoes and bread. He is exceptionally unemotional, rarely laughs or cries; his expression is stolid, but not stupid. He talks little but can understand both French and English. He is unable to walk without assistance, but can push a small chair about the ward.*

* Within a few days of the presentation of this report, the patient died of a rapidly progressive pneumonia. At autopsy the liver was found to weigh 2150 grams, which is about four times the normal weight at his age. The spleen was slightly enlarged. The heart, kidneys and endocrine glands were not grossly affected. The complete pathologic study will be published at a later date.

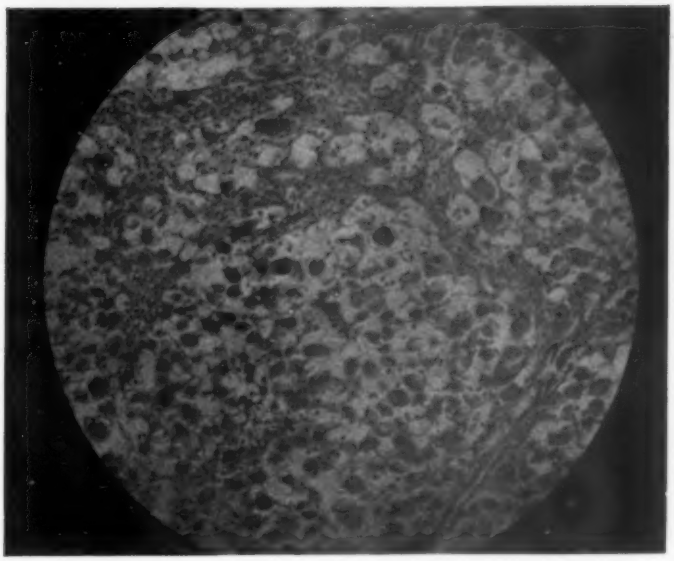


FIG. 3. Section of liver showing swollen parenchymal cells and early cirrhosis in the portal spaces. Alcohol fixed. Hemalum, erythrosin and saffron stain. × 60.

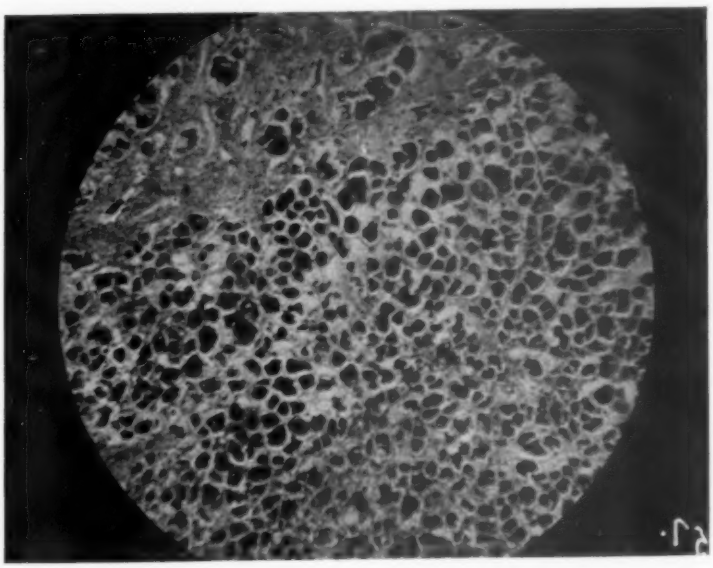
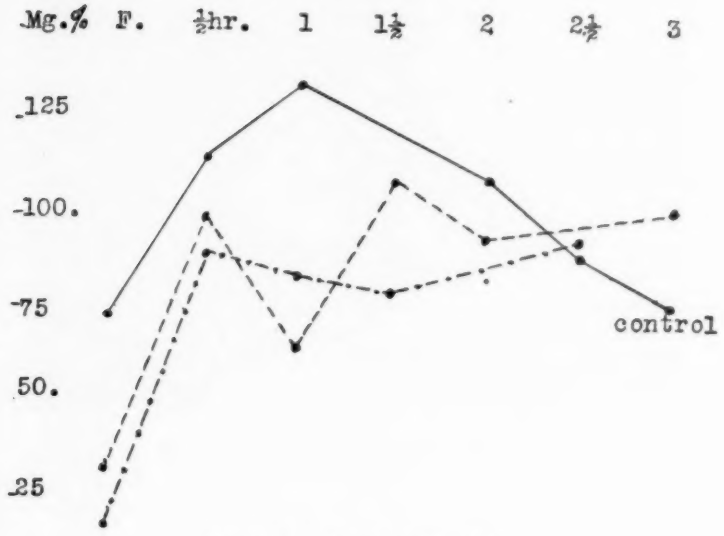


FIG. 4. Liver stained by Best's carmine method. Marked retraction of cells due to alcohol. Note the liver cells in the portal space at the top of the picture. These have been cut off from the rest of the lobule by the cirrhotic process. × 100.

Sugar Tolerance Curves.

After 18 grams Glucose by Mouth.

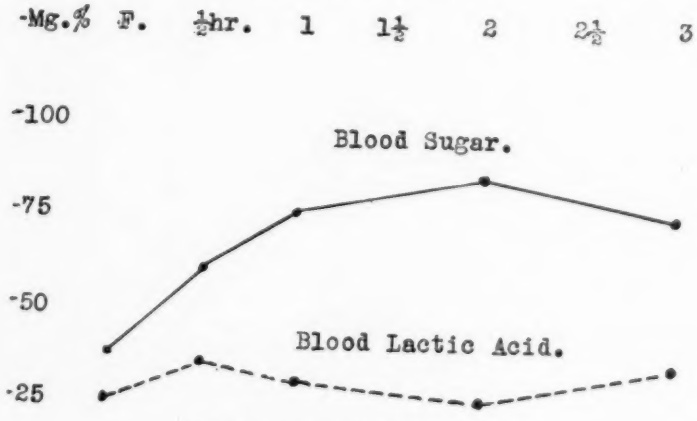
Patient P. B.



No glycosuria; no acetonuria.

Adrenalin Reaction.

After 0.5 c.c. 1/1000.



No glycosuria; slight acetonuria.

FIG. 5.

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DIVERTICULOSIS OF THE LARGE INTESTINE; AN EVALUATION OF HISTORICAL AND PERSONAL OBSERVATIONS *

By HAROLD C. OCHSNER, M.D., *Waukegan, Illinois,* and J. ARNOLD BARGEN, M.D., F.A.C.P., *Rochester, Minnesota*

THE nature and incidence of diverticula of the large intestine have offered a fertile field for study and speculation for several centuries.

Littre, in 1700, mentioned "diverticular hernia" without explaining it. Fischer has said that, although the first description of diverticula of the intestine is usually attributed to Sömmering in his translation into German of Matthew Baillie's "Morbid Anatomy," in 1794, Voigtel cited previous cases which had been recorded by Schröch, Riolan, Günz, Morgagni and Haller.

The subject of diverticula of the intestine was discussed by Cruveilhier in 1849. W. J. Mayo, Wilson, and Giffin, in 1907, were the first to record a group of cases in which actual demonstration of the pathologic changes, which occurred in diverticulitis, was established during life. In the same year, Moynihan called attention to the mimicry of carcinoma by diverticulitis. In 1909, Giffin and Wilson described the occurrence of peridiverticulitis, and in 1911, Wilson described in detail the pathology, pathogenesis, and complications of diverticulitis. In 1912, Giffin reviewed the clinical aspects of 27 cases of diverticulitis of the large intestine, in which operation had been performed at The Mayo Clinic from 1902 to 1912.

The first preoperative roentgenologic demonstration of diverticulitis is attributed to LeWald; the surgical aspects of this case were reported by Abbe in 1914. Comprehensive studies were reported by Rankin and Brown. The former observers noted an incidence of 5.67 per cent in 24,620 roentgenologic examinations of the colon. W. J. Mayo reported an incidence of 5.71 per cent in 31,838 examinations in the period from 1924 to 1930.

Erdmann expressed the opinion that the presence of diverticula in the intestine merits no greater attention than does that of the appendix or gallbladder. Bell [4] said that the condition of multiple diverticula, so-called diverticulosis, is perhaps chiefly of academic interest. Case described diverticulosis as a symptomless condition which commonly was encountered during roentgenologic examination of the alimentary tract. W. J. Mayo said that his observation that diverticulitis developed in 12 per cent of cases of diverticulosis was probably an overestimate, but Rankin and Brown discovered that this transition occurred in 17 per cent of their cases. Although diverticulosis itself is essentially an innocuous lesion, it appears to suggest a potential danger which should not be overlooked.

* Submitted for publication February 5, 1935.
From The Mayo Clinic, Rochester, Minnesota.

W. J. Mayo expressed the opinion that neither obesity nor constipation is a real cause of diverticulosis, and that muscular weakness of the colon is probably the underlying factor. Telling, who was one of the earliest observers, felt that deficiency of the muscularis was a factor. Lockhart-Mummery and Hodgson said that, among certain individuals who are past 45 years of age, there is a tendency for the muscle sheath to lose its tone, and that the earliest stage of diverticulosis is the formation of pulsion diverticula, which results from weakness of the musculature. Whether this weakness is congenital, acquired, or both, has not been determined, although many observers, especially E. T. Bell, believe that it is congenital in origin. The relationship of the blood supply to the development of diverticula is problematic. Graser's observation of the etiologic relation of venous stasis and enlargement of the foramina through which the vessels pass has not been confirmed.

It is a short step from the formation of diverticula to the production of an actual diverticulitis. Beer described the process as a formation of fecal masses in the diverticula, with pressure atrophy of the mucous membrane, and eventually ulceration and secondary infection. If, with edema of the walls, there results a closure of the orifices leading into the bowel proper, the stage is perfectly set. The explanation is so attractive that it seems remarkable that changes, which are the result of inflammation, do not occur more frequently in diverticula.

Personal Observations

Because a large number of patients, who have centered their symptoms about the intestine, present themselves for examination at the clinic in any given period, an unusual opportunity for investigation of this problem seemed at hand. The many conflicting opinions about the nature, incidence, and symptoms of diverticulitis and diverticulosis seemed to justify a statistical study of the cases which had been observed at the clinic in one year.

The relatively low incidence of diverticulosis of the colon is suggested by the fact that this condition was discovered to affect only 0.4 per cent of the patients who registered at the clinic in the selected year. This percentage is undoubtedly too low, as is indicated by the discovery of diverticula in 6.9 per cent of 447 cases which came to necropsy in the same period; in the majority of these cases the condition was not recognized during the clinical examination because the patients had no symptoms which were referable to the colon. The recognition of diverticulosis of the colon in 7 per cent of 2,747 patients, who were examined roentgenologically, ordinarily would not be considered indicative of the true incidence of this condition among the general population, because this group includes largely those patients who had symptoms which were attributable to the colon. However, this rate of incidence coincides almost exactly with that observed by the pathologist. In 11 per cent of the diverticula of the colon there was inflammation and diverticulitis at the time of examination. In almost 13 per cent of the cases

of diverticulosis, there was a history that was suggestive of previous diverticulitis.

TABLE I

Situation	Number	Per cent
Uncomplicated Diverticulosis (72.60 per cent of total cases)		
Sigmoid flexure	62	41.1
Sigmoid flexure and descending colon	26	17.2
Left half of colon	28	18.5
Entire colon	19	12.6
Ascending colon	3	2.0
Hepatic flexure	2	1.3
Ascending colon and sigmoid flexure	2	1.3
Cecum	2	1.3
Splenic flexure	2	1.3
Transverse colon	1	.7
Transverse colon and sigmoid flexure	1	.7
Left half of colon and cecum	1	.7
Right half of colon	1	.7
Right half of colon and sigmoid flexure	1	.7
Diverticulosis with history of diverticulitis (12.98 per cent of total cases)		
Sigmoid flexure	11	40.7
Sigmoid flexure and descending colon	10	37.0
Entire colon	4	14.8
Left half of colon	2	7.4
Total incidence of diverticulosis 85.58 per cent of total cases		
Uncomplicated diverticulitis (11.06 per cent of total cases)		
Sigmoid flexure	19	82.6
Sigmoid flexure and descending colon	2	8.7
Descending colon	2	8.7
Diverticulitis with perforation (2.40 per cent of total cases)		
Sigmoid flexure	4	80.0
Sigmoid flexure and descending colon	1	20.0
Diverticulitis with obstruction (0.96 per cent of total cases)		
Sigmoid flexure	2	100.0
Total incidence of diverticulitis 14.42 per cent of total cases		

Diverticula may be found in any portion of the gastrointestinal tract, and are not necessarily associated with similar abnormalities in any other portion. The preponderant occurrence of colonic diverticula in the sigmoid flexure is stressed by practically all writers on the subject. The relative frequency of involvement of various segments of the colon, as we found it, is given in table 1. The sigmoid flexure is most frequently involved in both diverticulosis and diverticulitis. Frequently, the involvement extends to the descending colon. The figures for diverticulosis roughly bear out the frequent statement that diverticula become more numerous toward the distal end of the colon.

The preponderant number of patients, who have diverticula of the sigmoid flexure, and who give histories that suggest diverticulitis, corresponds with the remarkably high incidence of active diverticulitis in the sigmoid flexure. When perforation or chronic obstruction occurred, it was invariably in the sigmoid flexure. One can only speculate as to the reasons for the high incidence of inflammatory changes in this situation. The theory of increased pressure in this region seems sound, but if one discards constipation and flatulence, as etiologic factors in the production of diverticula, it is difficult to explain why they should be effective in causing inflammatory changes.

Incidence, Sex, Age, and Build of Individual

The relative occurrence of diverticulosis and diverticulitis among the two sexes is of great interest. In the cases studied, diverticulosis was found as frequently among females as it was among males in the group of cases in which the condition was recognized clinically, although males predominated in the group of cases in which the existence of the lesions was first recognized by the pathologist. Males exceeded females in a ratio of 1.25 to 1 in the group of patients who gave a history of diverticulitis. Among the patients who had active diverticulitis at the time of examination, males outnumbered females 2.75 to 1. There were no females in the group with perforative or obstructive diverticulitis. All this would point to the fact that although uncomplicated diverticula of the colon affect women as frequently as they do men, the complications, and especially the serious complications, are more frequently observed among men. Alvarez's and Ascanio's study of 25,347 new patients, who registered at the clinic, indicated a ratio of males to females of 1.04 to 1. Our studies would seem to substantiate, therefore, the relative incidence by sex, which previously has been reported.

No instances of diverticulosis were found before the age of 30 years, among the cases studied. After the age of 30 years, the incidence of diverticulitis increased slowly in each half decade until that between the fifty-fifth and fifty-ninth years, which marked the peak of incidence for each sex. After this, the incidence decreased progressively. This is significant, inasmuch as Alvarez and Ascanio found that the curve, which represented the age of patients who registered at the clinic, reached its peak between the thirty-fifth and thirty-ninth years. There were only a few scattered cases of diverticulitis in which the patients were 50 years of age. After the age of 50 the distribution among men was practically equal in each half decade to the age of 70 years. There were only a few cases of diverticulitis among women; here the peak of incidence was in the seventh decade. The frequency of distribution of both conditions by decades for each sex is indicated in figures 1 and 2.

Reliable data in regard to height and weight of the patient were available in 51 cases of diverticulosis and in eight cases of diverticulitis. Comparison with a table of ideal weights revealed that there was practically an equal

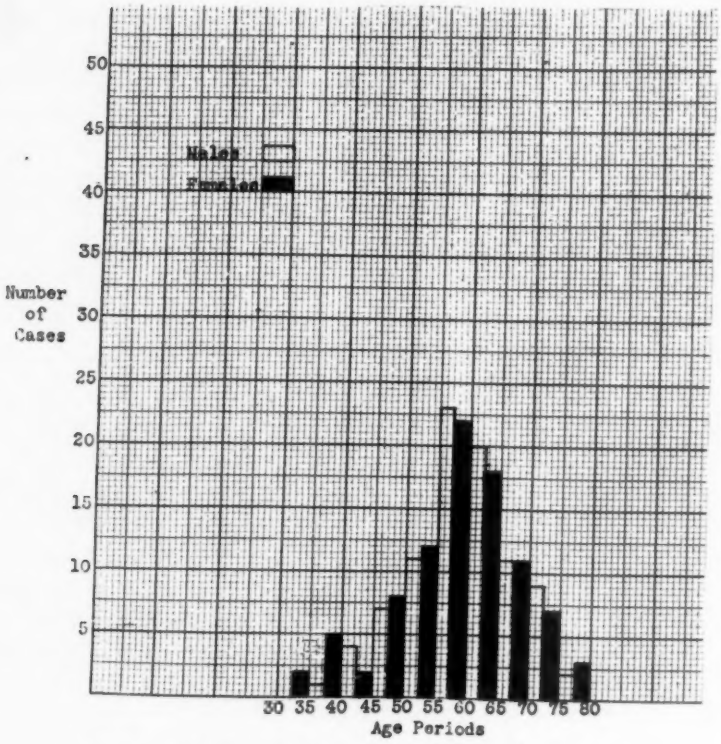

FIG. 1. The incidence of diverticulosis by half decades.

distribution of obesity and leanness. Eighteen of the patients who had diverticulosis were of normal weight, nine were 10 pounds overweight, and seven were 10 pounds underweight. Three of these patients were 20 pounds overweight and eight were a similar amount underweight; one was 30 pounds overweight and another was 40 pounds underweight. Only one patient was 50 pounds overweight. Among the patients who had diverticulitis, three were of normal weight, one was 10 pounds overweight and one was 10 pounds underweight. Two were 20 pounds overweight and one was 20 pounds underweight.

SYMPTOMS

The symptoms of diverticulosis in this series are enumerated in table 2. In the group of cases in which the sigmoid flexure was involved, constipation was present in 40 per cent while in 8 per cent there was diarrhea, which was present constantly in some, but only occasionally in other cases. Flatulence was a symptom in 21 per cent of the cases and abdominal pain was noted in 18 per cent. Pain was localized in the lower part of the abdomen, and varied in severity from a sense of fullness to cramping pains. Six per cent of the patients had noticed a narrowing of the diameter of the stool,

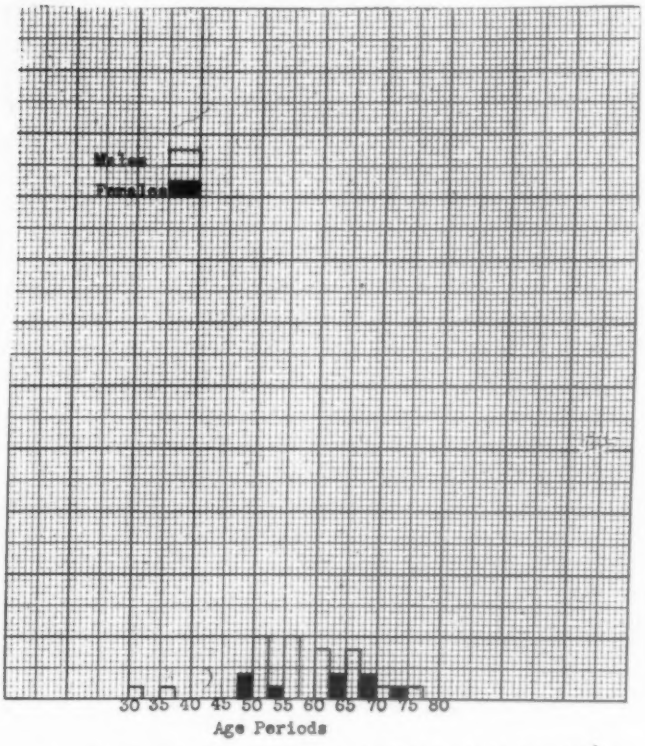

FIG. 2. The incidence of diverticulitis by half decades.

and an equal number had occasional rectal bleeding for which no cause was demonstrated. In 8 per cent of the cases, the clinical diagnosis was irritable intestine. This condition could account for the distress which was noted. Individuals who are severely constipated complain frequently of the smallness of their stools, and occasionally of slight bleeding. It can readily be seen that a majority of these cases of diverticulosis were devoid of symptoms which could be attributed to the diverticula.

Among the cases of diverticulosis which involved the sigmoid flexure and descending colon, 35 per cent of the patients complained of constipation of varying severity, and 31 per cent had mild diarrhea. Twenty-three per cent noted flatulence, and only 15 per cent had pain, which was a feeling of distress in the lower part of the abdomen and was relieved in half the cases by a bowel movement. Twelve per cent of the patients noted occasional rectal bleeding, which could not be accounted for by the presence of hemorrhoids.

In the cases of diverticulosis of the left half of the colon, constipation was noted in 29 per cent, diarrhea occurred in 14 per cent, and flatulence was present in 21 per cent. Abdominal distress, which was situated on the left side, was noted in two cases, or 7 per cent of the group. Constipation

TABLE II

Symptoms of Simple Diverticulosis

Situation	Total Cases	Constipation		Diarrhea		Abdominal Pain		Irritability		Flatulence		Blood	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Sigmoid flexure	62	25	40	5	8	11	18	5	8	13	21	4	6
Sigmoid flexure and descending colon	26	9	35	8	31	4	15			6	23	3	12
Left half of colon	28	8	29	4	14	2	7			6	21		
Entire colon	19	8	42			1	5			1	5	1	5
Miscellaneous	16	9	56	1	6	2	12	2	12	2	12		

Symptoms of Diverticulosis with History of Diverticulitis

Situation	Total Cases	Constipation		Diarrhea		Abdominal Pain		Irritability		Flatulence		Blood	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Sigmoid flexure	11	4	36	3	27	4	36			1	9		
Sigmoid flexure and descending colon	10	2	20	2	20	1	10			1	10		
Entire colon	4	2	50			1	25			1	25		
Left half of colon	2	1	50			1	50			2	100	1	50

was the principal symptom of the patients who had diverticulosis of the entire colon; it occurred in 42 per cent of the cases in this group. Only one patient (5 per cent of the group) complained of flatulence, and there was a similar incidence of lower abdominal pain and occasional rectal bleeding.

Of the remaining miscellaneous group, 16 in number, 56 per cent complained of constipation, which in one instance alternated with diarrhea. Only two complained of abdominal pain that could be attributed to the colon, and in each instance the patient was considered to have an irritable colon. Only two patients complained of meteorism.

In those cases of diverticulosis of the sigmoid flexure in which there was a history of diverticulitis, 63 per cent of the patients complained of irregularity of bowel movements; in 27 per cent of the cases there was some diarrhea, and in 36 per cent there was constipation. All of the patients, of course, gave a history of previous attacks of pain, but 36 per cent complained of abdominal pain at the time of examination, although there was then no evidence of diverticulitis. The pain was localized to the left lower quadrant of the abdomen, was dull in some cases, cramping in others, and was relieved to some extent by bowel movements. One patient, or 9 per cent, complained of flatulence. One patient had previously been operated on because of perforation and diverticulitis. Two patients, or 18 per cent, had no symptoms referable to the colon at the time of examination.

Among the patients who had diverticulosis of the sigmoid flexure and descending colon, and who presented a history of diverticulitis, 40 per cent complained of irregularity of bowel movements; there was an equal distribution of constipation and diarrhea. One patient, or 10 per cent, complained of gaseous distention, and in one case there was tenderness in the lower part of the abdomen. In two cases, or 20 per cent, colostomy had previously been performed for diverticulitis. Four patients, or 40 per cent of the total number, presented no gastrointestinal symptoms when examined.

Of the four patients who had diverticulosis of the entire colon and who gave a history of diverticulitis, two, or 50 per cent, presented no symptoms referable to the colon. Two, or 50 per cent, complained of constipation. One patient complained of gas; one had previously had diarrhea. Only one of these patients had pain at the time of examination. Of the two patients who had a demonstrated diverticulosis of the left half of the colon, and who gave a history of previous attacks of diverticulitis, one complained of tenderness in the left lower abdominal quadrant, which was relieved by a bowel movement or by the passage of gas; the other complained of constipation. Both patients had experienced discomfort from gas, and one had noted rectal bleeding.

The symptoms, which were observed in the cases of diverticulitis are enumerated in table 3. The most common symptom among the patients, who had uncomplicated diverticulitis of the sigmoid flexure, was pain, which occurred in 17, or 89 per cent of the group. It was usually associated with irregularity of the bowels, either diarrhea or constipation, and a variable

TABLE III

Symptoms of Simple Diverticulitis

Situation	Total Cases	Pain		Constipation		Diarrhea		Bleeding		Gas		Fever		Mass		Nausea and vomiting		Urinary	
		Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent	Cases	Per cent
Sigmoid flexure	19	17	89	11	58	5	26	4	21	3	16	5	26	1	5	1	5	3	16
Sigmoid flexure and descending colon	2	2	100	2	100			1	50	1	50							1	50
Descending colon	2	2	100	2	100														

degree of urgency of bowel movement. Frequently, the pain was relieved by bowel movement, and it occasionally was accompanied by rectal bleeding. Constipation occurred in 58 per cent of the entire group of cases; in one case there was an acute intestinal obstruction; diarrhea was noted in 26 per cent. The pain was localized to the left lower quadrant of the abdomen and was practically always intermittent and cramping in character. Occasionally, the pain extended to involve the entire abdomen. Three patients, or 16 per cent, complained of gaseous distention. In five, or 26 per cent of the cases, the patient complained of fever of variable degree, and in two cases there were chills as well. One patient had observed a lump in the left lower abdominal quadrant; there was a similar incidence of nausea and vomiting. Only three, or 16 per cent of the group, noted any urinary symptoms; in these cases there was a mild urgency of urination. Three patients had previously suffered attacks of diverticulitis.

In both cases of uncomplicated diverticulitis of the sigmoid flexure and descending colon, pain was noted in the left lower quadrant of the abdomen; both patients were constipated, and one had particularly observed a narrowing of the diameter of the stools, with a sense of obstruction and some gaseous distention. One had noticed some rectal bleeding. One had observed urinary frequency during the attacks. Both patients who had diverticulitis of the descending colon complained of pain in the left side of the lower part of the abdomen, and both were constipated. The patient who had diverticulitis of the rectosigmoid complained of pain in the lower part of the back, and was constipated.

All of the patients who had perforative diverticulitis of the sigmoid flexure of the colon complained of pain, which was localized in the left lower abdominal quadrant, cramping in character, accompanied by fever, and in half the cases, by chills. The cramps were often relieved by bowel movements, and sometimes by urination. Half of the patients complained of frequency and burning on urination. One patient was constipated and another had diarrhea. In one case there was a vesicosigmoid fistula. The one patient, who had perforating diverticulitis in the sigmoid flexure and descending colon, was constipated, and noted cramping pain and a tender mass in the left lower quadrant of the abdomen.

Both patients who had intestinal obstruction complicating sigmoid diverticulitis complained of pain in the lower part of the abdomen, which was cramping in character. This pain was accompanied in one case by diarrhea; in another case, by increasing constipation. One patient noted some rectal bleeding, the other had chills and fever.

Examination

Physical examination of the patients who had uncomplicated diverticulosis did not reveal any changes that could be attributed to the existence of this condition; the same was true of those who gave a history of previous diverticulitis. Among the 20 patients who had uncomplicated diverticulitis

of the sigmoid flexure, 10 had tenderness in the lower part of the abdomen; six had a mass in the lower quadrant of the abdomen or in the left side of the pelvis. Both patients who had uncomplicated diverticulitis of the sigmoid flexure and descending colon noted tenderness in the lower part of the abdomen; there was a palpable mass in one of these cases. Both patients who had diverticulitis of the descending colon and the single patient who had diverticulitis of the rectosigmoid disclosed tenderness in the left lower quadrant of the abdomen and a palpable mass. In all cases of perforative diverticulitis there was a tender mass in the left lower abdominal quadrant or in the pelvis, and the same was true of the patients who had chronic obstructive diverticulitis.

In the majority of writings on colonic diverticula, no mention is made of the value of proctoscopic examination in establishing the diagnosis. Only Fagge puts any faith in the method; he stated " more than a suspicion of diverticulitis may be established with the sigmoidoscope by the fixation and rigidity of the part of the pelvic colon affected." Proctoscopic examination was performed in 72 of the cases of diverticulosis, which we have studied. The occurrence of sacculation or fixation of the sigmoid flexure, or of demonstrable diverticula, confirmed the diagnosis in 15 cases, or 20 per cent of those examined. The observation of similar changes was made in 16 cases, or 64 per cent of the cases of diverticulitis. An interesting finding was the occurrence of polyps; three were situated in the rectum, six in the sigmoid flexure, and one in the rectosigmoid, making a total incidence of 14 per cent for the 72 patients who were examined by this method.

The most reliable method for demonstration of colonic diverticula is the roentgenologic examination. By the combined use of roentgenologic and proctoscopic examinations, practically all cases of diverticulosis can be detected, and most of these cases are impossible of clinical diagnosis. Certainly, although a clinical diagnosis of diverticulitis can usually be made with a fair degree of certainty, examination by a competent radiologist is the most accurate method of differential diagnosis in difficult cases. The opinion of the radiologist may be taken as of greater value than that of the clinician, or even that of the surgeon, who may actually have examined the lesion. There is some difference of opinion in regard to the relative value of the barium meal and the barium enema in roentgenologic examination; we prefer the latter.

Relation of Diverticulosis, Diverticulitis and Carcinoma

The relationship of diverticulitis to carcinoma of the colon has long been a matter of dispute. Early observers felt that diverticulitis was definitely an etiologic factor, but more recent writers seem to hold a view similar to that which was expressed by Rankin and Brown who found carcinoma in only four of 227 cases of diverticulitis which they studied. They expressed the opinion that the relationship of diverticulitis to carcinoma is probably

incidental rather than actual. We found malignancy of the colon in 6 per cent of the cases in which diverticula of the colon were discovered by clinical examination; the association was noted only among the patients who had diverticulosis, and who did not give a history suggestive of diverticulitis. In only seven of the 13 cases in which it was noted, was the malignancy in that portion of the colon in which the diverticula were found.

Treatment and Prognosis

The best treatment for diverticulosis consists of the avoidance of constipation and irritation; this is best accomplished by the use of a diet, which is bland and non-constipating, and which is free from residue. Mineral oil should be administered orally as a lubricant.

It is our practice to administer atropine in the form of tincture of belladonna to help relieve and avoid spasm. All cases of diverticulitis are associated with some peridiverticulitis, and the milder degrees of this change do not materially alter the outlook for the patient. The occurrence of the more serious complications, such as the formation of abscesses, with or without perforation, the formation of fistulas, peritonitis, and the occurrence of obstruction, which cannot be relieved by medical measures, constitute a clear indication for conservative surgery. Once such complications occur, the future is fraught with danger unless the intestine can be resected. However, some patients who had suffered complications, which have demanded colostomy, have recovered; the colostomy has been taken down, and no further trouble has been experienced.

The prognosis of simple diverticulosis is good, although some likelihood of inflammation exists. The prognosis of uncomplicated diverticulitis is rather good; most patients can be relieved by the medical measures which have been described previously.

Comment

It is difficult to determine the incidence of diverticula of the colon among the general population; there is a wide variation in the reports of necropsy. Although in the year 1933 the condition was recognized among only 0.4 per cent of the registrants at the clinic, it was found in almost 7 per cent of the necropsy reports for the same period. The diagnosis of diverticulosis depends on the roentgenologic examination. During the year which is covered by this investigation, 7 per cent of 2,984 patients, who were examined roentgenologically after they had received a barium enema, were discovered to have diverticulosis. This would suggest that these figures indicate the approximate incidence of diverticulosis. Diverticula are generally thought to affect males more often than they do females. In this group it was found that diverticulosis was evenly distributed among the two sexes, although diverticulitis, and particularly the complications of diverticulitis, occurred most frequently among males. It would seem, therefore, that colonic di-

verticula, like hypertension and many other conditions, are to be viewed with greater concern when they affect men than when they affect women. Although the occurrence of diverticula among children has been described, it is uncommon before the age of 40 years, and most common in the latter half of the sixth decade and first half of the seventh decade.

The etiology of colonic diverticula is still a matter of speculation. Among the etiologic factors, constipation and flatulence have been named, but the incidence of these symptoms has not been greater in the cases which we have studied than it would be among the general population. It is probable that obesity does not act as an etiologic factor; the majority of our patients were of normal weight.

It is probable that there is an inherent weakness of the muscular layer of the intestinal wall; whether this is inherited or acquired has not been determined. It is generally admitted that diverticula occur largely during the years of degenerative changes in the body. As previously stated, diverticulitis, or even diverticulosis, is exceedingly rare before the patient is 40 years of age. The possibility of the formation of diverticula as a senile change in an inherently weak muscular wall of the colon then suggests itself. The muscular weakness occurs in disseminated places, and affects patients who have been subjected to colonic strain and stress.

Diverticula are found with increasing frequency in the lower part of the intestinal tract. Diverticula are comparatively rare in the right half of the colon, and most common in the sigmoid flexure.

We have attempted in table 4 to classify the varieties and complications of diverticula of the colon as found in this series as well as in the literature. As can be seen, we consider that the so-called pre-diverticular stage is really a stage of diverticulosis; and we have found that a number of patients who had diverticulosis gave a history of previous diverticulitis. Diverticulitis, of course, may be acute, recurrent, or chronic. Peridiverticulitis, which frequently occurs in diverticulitis, may be simple or it may be associated with a variable degree of enterospasm. It is probable that peritonitis frequently occurs with diverticulitis but is usually not manifest; diverticulitis may be associated with abscess, or with perforation. Entero-visceral or entero-cutaneous fistulas may follow perforation. Rarely, metastatic suppuration occurs. With the healing of diverticulitis, adhesions may occur but they rarely produce obstruction. Although carcinoma of the colon may affect patients who have colonic diverticula, the association is probably accidental.

There are not any symptoms which are characteristic of diverticula, and recognition is dependent upon roentgenologic or proctoscopic examination. In a certain number of cases of diverticulosis, a history of previous attacks of diverticulitis can be elicited. The cardinal symptom of diverticulitis is pain, which usually is associated with irregularity of bowel movements, and which often is relieved by bowel movements. Pain is usually localized in the left lower quadrant of the abdomen, is of variable severity, and usually is intermittent and cramping. It may be accompanied by distention, chills

TABLE IV

Varieties and Complications of Diverticula of the Colon

I. Diverticulosis.
  A. Pre-diverticular stage of Spriggs and Marxer.
  B. Stage of formed diverticula.
    1. Asymptomatic.
    2. Symptomatic.
      a. History of previous attacks of diverticulitis.

II. Diverticulitis.
  A. Acute.
    1. Simple.
    2. Complicated.
      a. Peridiverticulitis.
        aa. Simple.
        bb. Enterospasm.
          1. Without obstruction.
          2. With acute obstruction.
            a. Partial.
            b. Total.
          3. With chronic obstruction.
      b. Peritonitis.
        aa. Local.
          1. Non-suppurative.
          2. With abscess.
            a. Perforation.
              aa. General peritonitis.
              bb. Fistulae, single or multiple.
                1. Entero-intestinal.
                2. Entero-vesical.
                3. Entero-cutaneous.
        bb. General.
      c. Resulting from lodgment of foreign body.
      d. Metastatic suppuration.
        aa. Septicemia.
        bb. Suppurative pylephlebitis or portal pyemia.
        cc. As a focus of infection.
  B. Recurrent.
  C. Chronic.
    1. Simple.
    2. Complicated.
      a. Peridiverticulitis.
        aa. Enterospasm.
        bb. Hyperplasia, with obstruction.
      b. Mesenteritis.
      c. Peritonitis.
        aa. Acute.
        bb. Recurrent.
        cc. Chronic.
          1. Adhesions.
            a. With or without angulation and obstruction.

and fever, dysuria, and urinary frequency. When perforation occurs, pain is more severe, often excruciating, and there are fever and chills. Urinary symptoms are frequent in the group with perforation, particularly if the perforation occurs anteriorly. When obstructive tumefaction occurs, there may be either constipation or diarrhea.

Physical examination of patients, who have diverticulosis, does not reveal any significant signs that can be referred to the colon. Patients who have diverticulitis usually have tenderness in the left lower quadrant of the abdomen, and often present a palpable mass. When perforation or obstruction occurs in diverticulitis, there is always a palpable mass; in the acute

phase, the tenderness may be so marked as to prevent adequate examination. Proctoscopic examination is of definite value, especially in cases of diverticulitis, in the acute phase of which one might fear to give a barium enema. Experienced observers can make a positive diagnosis by this method in 64 per cent of the cases. Roentgenologic examination is, of course, the most accurate means at our disposal for the detection of these lesions.

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INTERNAL MYXEDEMA; REPORT OF A CASE SHOWING ASCITES, CARDIAC, INTESTINAL AND BLADDER ATONY, MENORRHAGIA, SECONDARY ANEMIA AND ASSOCIATED CAROTINEMIA *

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THE classical picture resulting from diminished thyroid activity has long been recognized. But the fact that this endocrinopathy is generalized, involving the internal organs as well as the external covering and configuration of the body, is not so widely appreciated. Thus, alterations in the skin and hair, together with mental sluggishness, are relatively common findings. Occasionally cardiopathies occur for which no morbific factor other than an insufficient thyroid function can be found. More rarely abdominal ascites occurs as part of the syndrome of myxedema. Yet the literature contains a few reports of this finding for which no other etiology was demonstrated, and which disappeared under administration of thyroid substance.

In one such case, recently cited by Evans,[1] various chemical studies were made of the abdominal fluid. In addition, atony of the bladder (discovered accidentally when an attempted abdominal paracentesis yielded urine from a distended atonic bladder) was noted for the first time.

Our patient is considered of sufficient interest to report because she presented so many of the internal manifestations of myxedema with a paucity of the external signs. Both abdominal ascites and atony of the bladder were present. Chemical studies were made of the abdominal fluid in order that the figures obtained could be compared with those resulting from similar studies by Evans.

No other cause for any of the findings could be discovered, and the low basal metabolic rate, together with the marked improvement that resulted from the administration of thyroid substance apparently makes the diagnosis of hypothyroidism indubitable.

CASE REPORT

O. J., a 45 year-old, white, American farmer's wife was first admitted to the University of California Hospital on August 25, 1933.

Chief complaint—bloating and gas.

Family history—one sister had a carcinoma of the stomach.

Marital history—revealed that she had had four children. Two of these died in infancy and two were living and well. In addition there had been four miscarriages and the most recent pregnancy, two years before, had terminated in a still-birth.

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From the Department of Medicine of the University of California Medical School, San Francisco, Calif.

Past history showed pneumonia and smallpox in childhood, the usual childhood diseases, frequent sore throats prior to a tonsillectomy 19 years before, and a dry pleurisy six years before. She had been subject to attacks of migraine until 12 years before, and had always had very profuse menstrual periods lasting seven to eight days.

Present illness began 10 years prior to entry with the gradual development of pallor, weakness, sore and stiff joints, and finally ascites and edema of the ankles and face. Eight years before, she had entered a hospital for treatment. While there her abdomen was tapped, yielding a large amount of straw-colored fluid. She was told that her blood tested "60" and was discharged after five weeks with instructions to take a low protein diet. Since that time she had noted gradually progressive slowing of mental and physical activity. Her memory became poor and her speech slow. She also noted dry skin, lack of perspiration, intolerance to cold, and some loss of eyebrows and hair. For four or five years there had been increasing constipation, and she began to be troubled by bloating and gas. For two years she had had dull upper abdominal pain which affected her appetite; during this time she had lost 13 pounds. Her diet contained large quantities of vegetables, frequently carrots. The joint-pains persisted; her menstrual periods continued to be profuse (lasting eight to ten days) although somewhat irregular during the preceding year.

She finally visited the University of California Out-Patient Department where her basal metabolic rate was found to be minus 37 per cent and the blood hemoglobin (Sahli) 55 per cent (100 per cent equals 14.0 grams per 100 c.c.), with a red cell count of 2,700,000 per cu. mm. Gastric analysis after an alcohol meal showed free acid to 47 units and total acid to 57 units. She was then sent into the hospital.

Physical examination disclosed a patient who moved slowly and whose speech was slow and deliberate. The skin had a pale, slightly icteric tint, and was dry, cold, and somewhat rough. The hair was thin, dry, and scanty in the axillae. The eyebrows were sparse, especially the outer halves. The thorax was poorly clothed and the breasts atrophic. The heart showed enlargement both to the left and the right; the sounds were slow and of poor quality. There was a faint systolic murmur at the apex. Blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. The abdomen was distended both by gas and fluid, and there was marked diastasis recti with an umbilical hernia. No viscera or masses were palpable. Pelvic examination revealed no abnormality except a lacerated cervix and rectal examination showed internal hemorrhoids. There was slight pitting edema over the anterior tibial surfaces of the legs. There was no thickening of the subcutaneous tissues nor were there any of the fat pads commonly noted in hypothyroidism.

Laboratory Data

Basal Metabolic Rate: Minus 37 per cent and minus 41 per cent.

Blood: Hemoglobin (Sahli) 50 per cent; red blood cells 3,160,000 per cu. mm.; white blood cells 4,400 per cu. mm., with a normal differential count.

Urine: Specific gravity 1.010; albumin, very slight trace; sugar, 0; sediment, showed an occasional pus cell.

Stool: Negative for ova, parasites and occult blood.

Phenolsulphonephthalein Kidney Function Test: 50 per cent excretion in 380 c.c. of urine 2 hours and 10 minutes after intramuscular injection.

Blood: Kahn: Negative.

Plasma cholesterol—238 mg. per cent.

Serum proteins—Total: 6.46 gm. per cent; albumin, 3.90 gm. per cent; globulin, 2.56 gm. per cent; ratio, 1.52.

Sugar (fasting): 70 mg. per cent.

Non-protein nitrogen: 29.8 mg. per cent.

Chlorides (as NaCl in plasma): 523 mg. per cent.

Icterus index: 15.
Carotin: 2 plus.
Venous Pressure (direct method): 80 mm. of water.
Venous Pressure (indirect method): 95 mm. of water.
Glucose Tolerance Test: Blood sugar, fasting, 77 mg. per cent.
30 minutes, 137 mg. per cent.
60 minutes, 156 mg. per cent.
120 minutes, 148 mg. per cent.
Rose Bengal Liver Function Test *:
Specimen I (8 minutes), 62 per cent retention
Specimen II (16 minutes), 44 per cent retention
(Upper limits of normal are: I—50 per cent, II—35 per cent)
Residual Urine: 100 c.c.

ROENTGEN-RAY STUDIES

(Interpreted by Dr. R. S. Stone)

Chest Films: The heart was enlarged in all directions, more to the left. There was a point of adhesion over the left diaphragm.

Gastrointestinal Series: The stomach was displaced forward by a questionable soft tissue mass. There was evidence of periduodenal adhesions.

Barium-Enema: The colon was voluminous and atonic.

Intravenous Cholecystograms: The gall-bladder visualized and functioned normally. There was evidence of adhesions around the cystic duct.

Electrocardiogram: Rate 51 per minute, P–R interval 0.22 second, small QRS complexes.

Abdominal Paracentesis: This was performed with some difficulty and only 150 c.c. of amber-colored fluid were removed. This had a specific gravity of 1.012 and contained 4,400 red blood cells and 100 white blood cells per cu. mm. of which 75 per cent were mononuclear cells and 25 per cent were polymorphonuclear cells. The chemical composition of the fluid was as follows:

Protein: Total, 3.88 gm. per cent
Albumin, 2.31 gm. per cent
Globulin, 1.57 gm. per cent Ratio 1.47
Sugar: 112 mg. per cent
Non-Protein Nitrogen: 23 mg. per cent
Chlorides (as NaCl): 648 mg. per cent
Cholesterol: 96 mg. per cent

Course: After preliminary studies were completed, the patient was placed on a carotin-free diet, and the oral administration of Armour's desiccated thyroid was begun at 0.065 gm. twice daily. After 12 days of medication the basal rate had risen to minus 19 per cent. The thyroid-dosage was then increased to 0.065 gm. three times daily which was continued until she left the hospital eight days later. Just before discharge the basal rate was minus 26 per cent. The plasma cholesterol had dropped to 134 mg. per cent. A roentgenogram of the chest at this time showed the heart to be slightly diminished from the previous size, especially in the antero-posterior diameter; an electrocardiogram showed little change. The blood counts remained practically stationary, but the albuminuria had cleared completely; the blood-serum had become carotin-free. The icterus index had dropped to 8. The blood pressure remained low, reaching above 100 systolic on only one occasion. A low temperature (35° to 36° Centigrade) tended to rise to normal under therapy; the pulse paralleled this, increasing from a rate of 50–60 per minute to 70–80. The patient's weight which was fairly well stabilized at 62.7 kilograms (137.9 pounds) before

* By method of Althausen, Biskind and Kerr.[2]

medication was started, had dropped to 57 kilograms (125.4 pounds) on discharge 20 days later.

At this time there was very little symptomatic improvement and the patient was instructed to increase her thyroid dosage to 0.065 gm. four times daily. She was discharged from the hospital on September 13, 1933.

Interval History: The patient returned to the clinic one month after leaving the hospital stating that there had been marked improvement in general well-being. Her skin was smoother and she perspired occasionally. She had had one menstrual period which had lasted only three or four days and had been relatively scanty in contrast to her former menorrhagia. Her appetite had improved and she had ceased losing weight.

She now appeared more alert, though still pale. There was no icterus. The heart had diminished to normal size, the rate was 84, and the sounds were forceful in character. No ascites or abdominal distention could be found. There still remained slight edema of the ankles.

Laboratory Data

Basal Metabolic Rate: Plus 7 per cent (minus 41 per cent before treatment).

Plasma Cholesterol: 144 mg. per cent (238 mg. per cent before treatment).

Blood: Hemoglobin (Sahli) 55 per cent; red blood cells 2,810,000 per cu. mm.; white blood cells 6,100 per cu. mm.

Urine: Negative; specific gravity 1.006. Sediment showed a rare white blood cell.

Roentgenogram of the chest revealed a marked diminution in heart size (4.9 cm. less in the transverse diameter) with pulsations of good tone.

Electrocardiogram: Rate 80, P–R interval 0.16 second, QRS complexes were of greater amplitude and there was marked improvement in the T-waves.

Second Hospital Admission: The patient was readmitted to the hospital for further study on November 20, 1933, one month after her last visit to the clinic and two months after her first discharge from the hospital.

She stated that the improvement had been maintained, although her constipation was unchanged. She still noted palpitation occasionally on exertion and ankle edema late in the day.

Physical examination was essentially as before. The skin had a more yellow tint. The heart was normal in size to percussion and the sounds were of good quality, rate 72. The abdomen showed moderate distention. There was no ascites and no edema of the extremities.

Laboratory Data

Basal Metabolic Rate: Plus 3 per cent.

Blood: Hemoglobin (Sahli) 45 per cent; red blood cells 2,800,000 per cu. mm.; white blood cells 6,950 per cu. mm.

Urine: Specific gravity 1.010; albumin 0; sugar 0; sediment showed an occasional white blood cell.

Blood: Plasma cholesterol: 151 mg. per cent.

Serum proteins: Total, 6.12 gm. per cent.
Albumin, 4.18 gm. per cent.
Globulin, 1.94 gm. per cent.
Ratio 2.15

Venous pressure (direct method): 120 mm. of water.
Venous pressure (indirect method): 85 mm. of water.
Icterus index: 11.
Carotin: 3 plus.
Glucose Tolerance Test: Blood sugar, fasting, 108 mg. per cent.
30 minutes, 186 mg. per cent.
60 minutes, 218 mg. per cent.
120 minutes, 141 mg. per cent.
Rose Bengal Liver Function Test:
Specimen I (8 minutes), 53 per cent retention.
Specimen II (16 minutes), 32 per cent retention.
Residual Urine: 45 c.c.

ROENTGEN-RAY STUDIES

Chest: This showed the improvement in heart size and tone to be well maintained.

Gastrointestinal Series: No evidence of the previously noted forward displacement of the stomach could be found. The former impression of a mass behind the stomach was now considered to have been due to an excess of gas in the large atonic splenic flexure of the colon.

Barium Enema: There was still evidence of a voluminous large bowel. However, voluntary evacuation after the enema showed much better emptying than after a similar attempt two months before.

Course: During this hospital stay of six days her weight dropped from 60 kilograms (132 pounds) to 55.6 kilograms (122.3 pounds). Inasmuch as there had been no improvement in the anemia, iron and ammonium citrate 1.0 gm. three times daily was prescribed. She was told to continue her thyroid-dosage of 0.065 gm. four times daily.

Clinic Visit—January 16, 1934: The patient returned to the clinic seven weeks after her second discharge from the hospital, reporting that she felt quite well and much stronger. The dyspnea, palpitation, and edema had completely disappeared. Menstrual periods continued to occur regularly but were relatively scanty, lasting only three or four days. The constipation was unchanged. The weight had increased gradually to 64.3 kilograms (141 pounds)—a gain of 8.7 kilograms (19.1 pounds).

Ascites and edema were absent. The blood pressure was 120 mm. Hg systolic and 74 diastolic.

Blood counts showed: Hemoglobin (Sahli) 76 per cent; red blood cells 4,660,000 per cu. mm.; white blood cells 6,800 per cu. mm.

Carotin was one plus in the blood serum.

No alteration in treatment was considered necessary, consequently she was advised to continue only with desiccated thyroid and iron.

Clinic Visit—February 16, 1934: The patient's well-being had been maintained. Constipation was unchanged. She had had one menstrual period which had lasted three days with scanty flow. The pulse rate was 72 per minute. Blood pressure was 110 systolic and 60 diastolic.

Basal metabolic rate, plus 1 per cent. Blood—hemoglobin (Sahli) 80 per cent; red blood cells 4,450,000 per cu. mm.

She was advised to continue treatment and pursue normal activities.

Third Admission to Hospital—August 30, 1934: Six and one-half months after her last visit, the patient was readmitted to the hospital as an emergency.

She had been feeling quite well and doing all of her housework until two months before. At that time she undertook some part-time work in a cannery near her farm, which after a short while was increased to full-time. This work in addition to her household duties made a daily schedule of 16 to 17 hours labor. Five weeks before entry, after two weeks of this exhausting regime, she was awakened one night by a feeling of nausea and a dull generalized abdominal ache. She developed some weakness and anorexia and noted mucus in her stools. Then she felt better for two or three days, but on trying to return to work, developed severe epigastric and right lower abdominal pain accompanied by nausea and protracted vomiting. She was

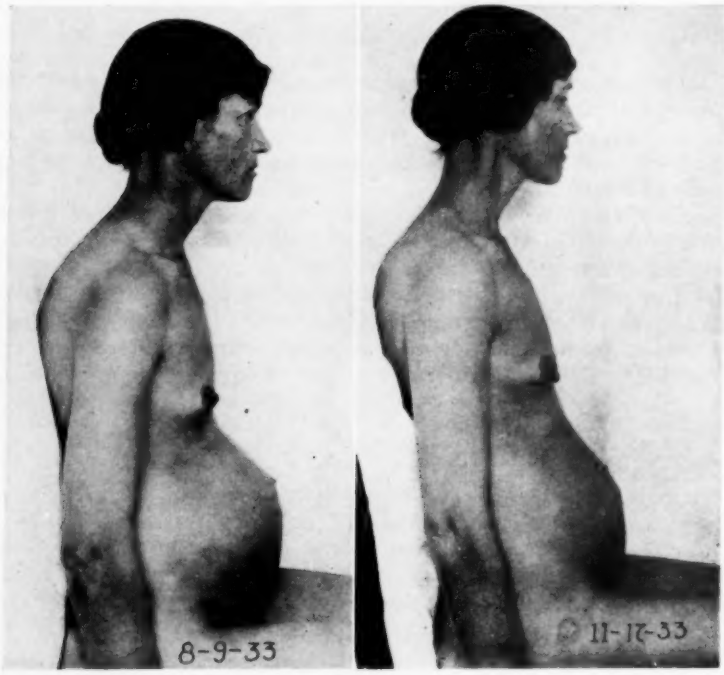

FIG. 1. Comparative views of the patient showing her general appearance and the diminution in abdominal distention after treatment was instituted.

said to have regurgitated food eaten 36 hours previous. She was hospitalized for eight days, obtaining gradual relief from enemata and cathartics. Once again she returned to work. However, all the severe symptoms recurred and, after two weeks of nausea and frequent vomiting, she was again brought to San Francisco and admitted to the University of California Hospital. After the onset of these acute symptoms five weeks before she had taken thyroid only irregularly, and at the time of entry she had had none for four weeks.

On examination she was still nauseated, vomiting frequently, and obviously dehydrated. The abdomen showed visible peristalsis and tenderness in the right upper quadrant.

Some improvement resulted from the administration of fluid parenterally and glucose intravenously so that four days later a barium enema was given, followed by barium orally. Under the roentgen screen there was evidence of partial obstruction of the jejunum.

A subcutaneous injection of Pitressin caused a marked increase in visible peristalsis followed by a reproduction of the nausea and abdominal pain. It was then decided to perform an exploratory laparotomy which was done on September 7, 1934, by Dr. Leon Goldman.

On opening the abdomen a small amount of colorless free fluid escaped. The small and large intestines appeared normal throughout. The appendix, liver, kidneys, and pancreas were apparently normal. The gall-bladder was slightly thickened; there were a few periduodenal adhesions. The uterus was somewhat enlarged and soft. The appendix was removed.

The postoperative course was uneventful. A menstrual period started two days later at the regular interval. Pelvic examination immediately afterward was normal and a Friedman test for pregnancy was negative. The conclusion was reached that the enlarged and soft uterus noted at operation was due to pre-menstrual congestion.

Since the patient had not had any thyroid substance for over five weeks, it was planned to utilize this opportunity as a control period and, as soon as her condition warranted, to repeat most of the laboratory studies. Unfortunately she was not directly under the authors' care; thyroid was prescribed and she received 0.065 gm. eight times in three days before it was discontinued. Basal rate taken then was 9.3 per cent minus. After another week without thyroid the following laboratory work was done:

Basal Metabolic Rate: Minus 22 per cent.

Blood: hemoglobin (Sahli) 85 per cent; red blood cells 4,700,000 per cu. mm.; white blood cells 10,700 per cu. mm.

Plasma cholesterol: 200 mg. per cent.

Serum proteins: Total, 4.8 gm. per cent.
albumin, 3.22 gm. per cent.
globulin, 1.57 gm. per cent.
Ratio 2.05.

Icterus index: 11.

Carotin: Negative.

Glucose Tolerance Test: Blood sugar, fasting, 82 mg. per cent.
30 minutes, specimen lost.
60 minutes, 137 mg. per cent.
120 minutes, 84 mg. per cent.

Rose Bengal Liver Function Test:
Specimen I (8 minutes), 78 per cent retention.
Specimen II (16 minutes), 60 per cent retention.

Residual Urine—500 c.c.

Roentgen films and fluoroscopy of the chest showed the heart to be normal in size and the beats of good tone.

Electrocardiogram showed a rate of 60 per minute. The P–R interval was 0.18 second. The QRS complexes and T-waves were of small amplitude.

The body temperature tended to be low as did the rate of the pulse and respiration.

The patient was discharged on September 20, 1934, with instructions regarding limited activity and the resumption of thyroid substance, 0.065 gm. twice daily. This dose, however, was to be increased gradually as indicated.

Discussion

Ascites. The rarity of ascites as a manifestation of myxedema has already been noted. However, several reports can be found in the literature. Mussio Fournier [3] reported five cases, two of which had associated hydrothorax. He quotes Nothnagel as publishing a similar case. Marsh [4]

O.J. Outline of Laboratory Work.

	8/25/33.	9/25/33.	10/23/33.	11/20/33.	1/16/34.	2/16/34.	9/19/34.
B.M.R.	40% minus	26% minus	7% plus	3% plus	—	1% minus	22% minus
Plasma Cholesterol	238 mg.%	134 mg.%	144 mg.%	151 mg.%	—	—	200 mg.%
Icteric Index	15	8	—	11	—	—	11
Blood Carotin	2 plus	Neg.	—	Neg.	1 plus	—	Neg.
Blood—Hgb	50%	47%	55%	45%	76%	80%	85%
RBC	3,160,000	3,240,000	2,810,000	2,800,000	4,660,000	4,450,000	4,280,000
WBC	4,400	—	6,160	6,950	6,800	—	7,120
Urine—Albumin	2 plus	Neg.	Neg.	Neg.	—	—	Neg.
Residual Urine	100 c.c.	—	—	45 c.c.	—	—	500 c.c.
Rose Bengal Test—Retention—							
I	62%	—	—	53%	—	—	78%
II	44%	—	—	32%	—	—	60%
EKG—Rate	51	60	80	60	—	—	60
P–R Interval	0.22 sec.	0.22 sec.	0.16 sec.	0.19 sec.	—	—	0.18 sec.
Glucose Tolerance Test—							
I	77 mg.%	—	—	108 mg.%	—	—	82 mg.%
II	137	—	—	186	—	—	—
III	156	—	—	218	—	—	137
IV	148	—	—	141	—	—	84
Blood Pressure	90/50	90/48	—	114/56	120/74	110/60	120/70
Weight	63.2 Kg.	57.0 Kg.	57.5 Kg.	60.1 Kg.	64.3 Kg.	64.4 Kg.	52.1 Kg.
Temperature	36°C.	36.5°C.	—	37°C.	—	—	36°–37°C.
Pulse	50–60	70	84	80	84	72	50–60
Respirations	18	20	—	20	—	—	11–17

CHART 1. Outline of the laboratory findings during the thirteen-month period of observation.

reported another case. Six questionable instances were presented by Davidson [5] who labeled them "thyroid nephrosis." Beretervide and Herrera [6] report a case which seems typical clinically but whose basal metabolic rate was only minus 15 per cent. The recent report of Evans [1] has already been referred to.

The finding of ascites is especially interesting in this patient because of its reported presence eight years before. Although the second abdominal paracentesis was unsatisfactory and yielded only 150 c.c. of fluid, physical signs indicated the presence of a much larger amount. These signs completely disappeared after seven weeks of thyroid-therapy and there was no further evidence of fluid until the exploratory laparotomy revealed a small amount after four weeks without thyroid.

Other causes for the ascites could be excluded. The duration of eight years made it improbable that either carcinoma, cirrhosis or tuberculosis was responsible. This was borne out by the negative findings at exploration. No evidence of nephritis was found—the only urinary abnormality being an albuminuria which disappeared under thyroid-therapy. The proteins of the blood serum were found to be normal both before and after the beginning of treatment, so osmosis was probably not a factor. The possibility of cardiac decompensation with venous congestion was an important one, especially in view of the enlarged heart found on admission. However, the venous pressure was normal in four determinations and no other evidences of congestive failure were found. The above findings, combined with the facts that the ascites vanished on thyroid-therapy, and reappeared after thyroid was omitted, make it reasonable to assume that hypothyroidism was the etiologic factor.

Evans [1] after using approximately similar precautions likewise reached the conclusion that the ascites in his patient was of myxedematous origin. It is interesting, therefore, to compare the properties and chemical content of the fluids obtained by him and us. The following table also includes the recorded findings on the fluids from the patients reported by Beretervide and Herrera [6] and by Mussio Fournier.[3]

The specific gravity was high in Evans' case. In the case of Beretervide and Herrera the strongly positive Rivalta also classes the ascitic fluid obtained by them as an exudate. However, in our patient the fluid had a relatively low specific gravity. Mussio Fournier reports a negative Rivalta in one case and definitely calls the fluids from three of his other cases transudates. Evans found a relatively high total protein and Beretervide and Herrera obtained a high figure for albumin content. In the case here reported the proteins were lower.

Epstein [7] found the average protein content in nine ascitic fluids due to cardiac decompensation to be 3.3 gm. per cent. Salvesen and Linder [8] reported values of 2.6 and 2.2 gm. per cent in two cases of cardiac ascites. Foord, Youngberg and Wetmore,[9] after examining the ascitic fluid from 10 cases of cirrhosis and eight of cardiac decompensation, obtained an

	O.J. (1933)	Evans (1932)	Beretervide and Herrera (1932)	Mussio Fournier (1925)
Specific Gravity	1.012	1.020	Strongly positive Rivalta	1 negative Rivalta
Cells	75 mononuclear leukocytes 25 polynuclear leukocytes 4,400 red blood cells	77 mononuclear leukocytes 335 red blood cells	85 per cent lymphocytes	3 "transudates" Endothelial cells
Total Protein	3.88 gm. %	5.1 gm. %		
Albumin	2.31 gm. %	2.9 gm. %	7.6 gm. % (by refractometer method)	
Globulin	1.57 gm. %	2.2 gm. %		
Non-Protein Nitrogen	23 mg. %	23 mg. %		
Chlorides (as NaCl)	648 mg. %			
Cholesterol	96 mg. %			
Sugar	112 mg. %			

average specific gravity of 1.012 and an average protein content of 1.32 gm. per cent and 1.69 gm. per cent respectively in the two groups. Macheboeuf and Fethke [10] report protein values averaging 4.22 gm. per cent in the ascitic fluid of two patients with cardiac disease and 1.65 gm. per cent in two patients with alcoholic cirrhosis. The value of 3.88 gm. per cent reported in this case is therefore higher than the average findings in transudates, but not as high as that reported by Evans.[1]

The values for non-protein nitrogen, chlorides, cholesterol, and sugar fall within the average range found in ascites due to cirrhosis and cardiac decompensation (Foord et al.[9] and Macheboeuf and Fethke [10]).

Foord and associates [9] have noted that in fluids with high specific gravity there is a proportional increase in the protein, and the Rivalta test becomes increasingly positive. When this fact is applied to the findings in the table above, it is apparent that there is considerable variation in the composition of ascitic fluid recovered from patients with myxedema. Whether or not this fluid is true "myxedematous fluid" is a speculative question, but if so, then one of the characteristics of such fluid is a varying composition.

Atony of the Bladder. The association of urologic symptoms with myxedema was commented on long ago. However, Beck,[11] in 1927, studied 100 cases particularly from this standpoint. He noted the frequency of nocturia, pollakiuria, dysuria, oliguria and incontinence, and stated that the urinary sediment usually showed large numbers of epithelial cells from the bladder and frequently pus. The accidental discovery by Evans,[1] of atony of the bladder with residual urine, gives an obvious explanation for all these symptoms and signs. The atony in his patient was so marked that the bladder had not been able to empty itself, even after preliminary catheterization with a short catheter.

Although the atony in our case was not marked, only 100 c.c. of residual urine being obtained at first, there was definite improvement on thyroid-therapy. Three months after thyroid was started the residual had decreased to 45 c.c. The postoperative residual of 500 c.c. was considered as resulting largely from the surgical procedure.

It seems probable that more frequent observations will reveal this to be a common finding in hypothyroidism. In view of the frequent and characteristic cardiac and intestinal atony, it is not so much surprising that bladder atony also occurs, but that this phenomenon was not noted many years ago.

Cardiac Atony. There have been numerous case reports and discussions in the literature since Zondek [12] first described "Das Myxödemherz" in 1918. Recent excellent reviews of this subject can be found in papers by Lisser and Anderson,[13] Ayman, Rosenblum and Falcon-Lesses,[14] Gallagher,[15] and Lerman, Clark and Means.[16] The original description by Zondek is of a symmetrically enlarged flabby heart with slow feeble action under the fluoroscope, but without evidences of decompensation. Many of the reported cases are of this type. Under thyroid-therapy these hearts shrink to normal.

In 1925 Fahr [17] reported a patient in whom congestive failure was a marked feature, and another group of reported cases belongs to this class. Thyroid in such cases results in great improvement.

A third group, however, shows an accompanying advanced arteriosclerosis. Attempts at thyroid-therapy, by raising the metabolism and cardiac rate, place an increased strain on the myocardium which may result in marked cardiac embarrassment and even coronary thrombosis. Christian,[18] and Sturgis and Whiting [19] called attention to this possibility.

Fishberg,[20] Christian,[18] and Duden [21] have called attention to the high incidence of early arteriosclerosis in myxedema, while Thompson, Dickie, Morris and Hilkevitch [22] have noted the high incidence of hypertension. It is, therefore, possible that the three groups of cardiac complications outlined above (i.e., (1) atony without decompensation, (2) atony with decompensation, and (3) atony with decompensation and advanced arteriosclerosis) are progressive stages of the same process. Apparently the important etiological factor in the first group is hypothyroidism, but as the cardiac picture progresses, arteriosclerosis plays a gradually increasing rôle.

The heart findings in the case here reported place it in the first group of atony without decompensation. Roentgen-ray examination showed the heart to be enlarged in all chambers. The rate was slow and by fluoroscopy the myocardium appeared flabby, the beats feeble and of poor tone. Auscultation disclosed the heart sounds to be of poor quality. After six weeks of thyroid-therapy the heart had diminished in size in all diameters, and the transverse diameter was decreased by 4.9 cm. (figure 2). The rate had increased and the beats were seen to be of good tone. There was

a coincidental improvement in the quality of the heart sounds. No loss in tone could be detected after thyroid had been discontinued for five weeks, although the rate was slower.

The electrocardiographic changes were fairly pronounced, although not as marked as many of those which appear in the literature. The changes most frequently noted are low, diphasic, or inverted T-waves in one or more leads. According to Thacher and White [23] and Lisser [24] this occurs most frequently in Lead II, but Fahr [25] states that it is more common in Lead I. Low electromotive force resulting in decreased amplitude of the QRS complexes has been stressed by many writers, and Fahr [25] has frequently noted

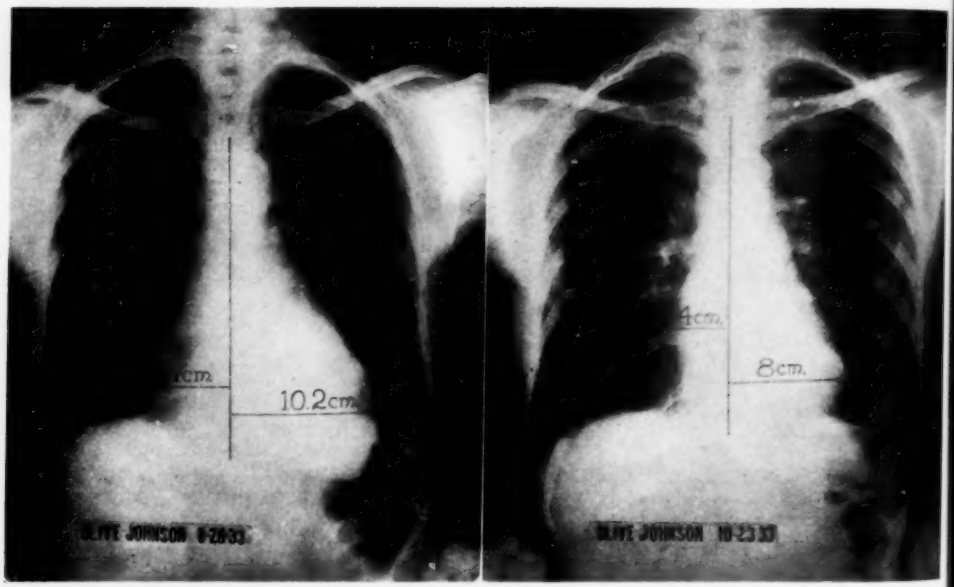

FIG. 2. Typical myxedema heart with enlargement of all chambers. The shrinkage in heart size under therapy is quite apparent, with a difference of 4.9 cm. in transverse diameter after two months of treatment. Under the fluoroscope the beats were of markedly improved tone at the second examination.

a negative QRS complex in Lead III. Absent or diminished P-waves were first noted by Zondek [12] in his original paper and have been reported frequently since. Slurring of the QRS complexes and prolongation of the P–R interval are other changes that have been occasionally noted. The changes, however, have been variable in the reported cases.

The effect of the increased resistance of the skin in myxedema has been a source of conflicting reports. Nobel, Rosenblüth and Samet [26] reported the presence of P- and T-waves in tracings taken from the anterior chest wall using needle electrodes after they had been absent in the usual leads from the extremities. Lerman, Clark and Means,[16] however, using both needle electrodes and standard contact electrodes in a series of instances, found little change in the tracings.

Before treatment (figure 3) the tracings from our case showed a sinus bradycardia, small P-waves in Leads I and III, prolonged P–R interval (0.22 second), low amplitude of the QRS complexes, small T_1, and small diphasic T_3. After two months of treatment the T-waves had become more pronounced, there was increased amplitude of the QRS complexes, and the rate had increased to 84 per minute. These changes were definite, and although not as striking as some of those reported, they are considered characteristic of "myxedema heart."

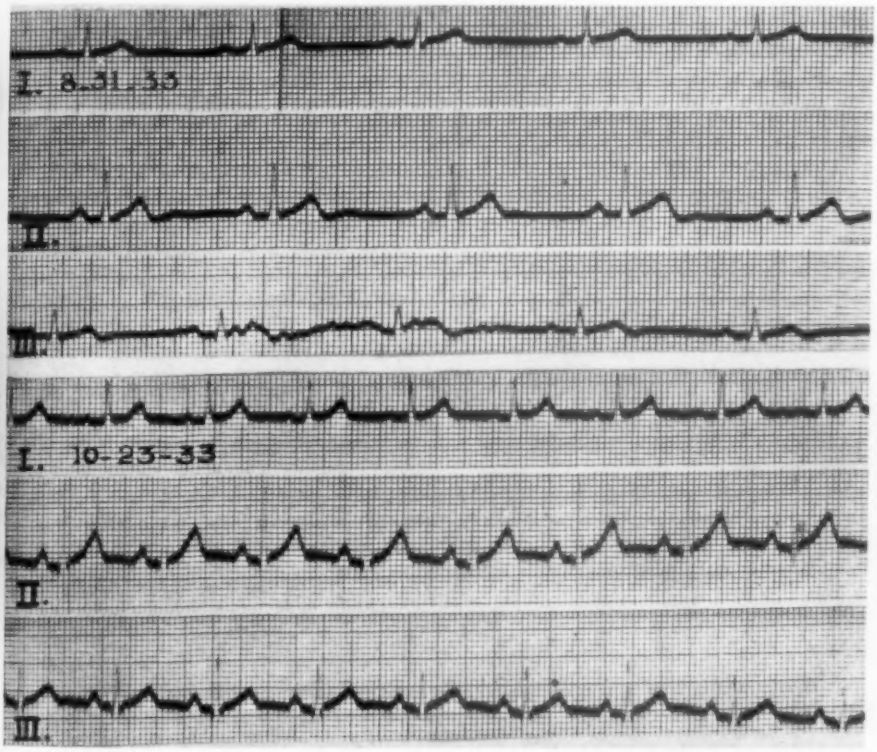

FIG. 3. Electrocardiographic tracings showing the following effects of treatment: (1) increased rate, (2) increased amplitude of the P-waves, QRS complexes, and T-waves, and (3) decreased P–R interval.

After thyroid had been discontinued there was some reversion to the former type with decreased amplitude of the QRS complexes and T-waves, slowing of the rate, and slight prolongation of the P–R interval.

Intestinal Atony. Constipation is an almost constant finding in hypothyroidism. Mathers [27] demonstrated atony of the colon by roentgen-ray which improved with thyroid-therapy, and Deusch [28] showed experimentally that thyroid caused increased intestinal tonus, both in experimental animals and in man. Brown [29, 30] noted the occasional marked improvement in pa-

tients complaining of intractable constipation after thyroid medication and found such patients to have low basal metabolic rates. Wohl [31] describes the condition as the " lazy bowel of myxedema," and Lisser [24] emphasizes its frequency.

The fact that the abdominal complaint of " bloating and gas " is the one that brought our patient to the clinic for medical attention demonstrates the importance to the patient of this phase of the disease. The symptoms were probably partly due to the ascites and partly due to the atonic bowel. It is also noteworthy that a " questionable mass behind the stomach, causing forward displacement," was reported after the first roentgen-ray examination of the gastrointestinal tract. Subsequent examination proved this " mass " to be gas in the distended splenic flexure of the colon.

The findings after barium enema demonstrated clearly the effect of the thyroid-therapy on the colon. Following the enema the patient was told to expel voluntarily as much as she could of the enema material, after which another film was taken. As shown in figure 4, at first very little of the

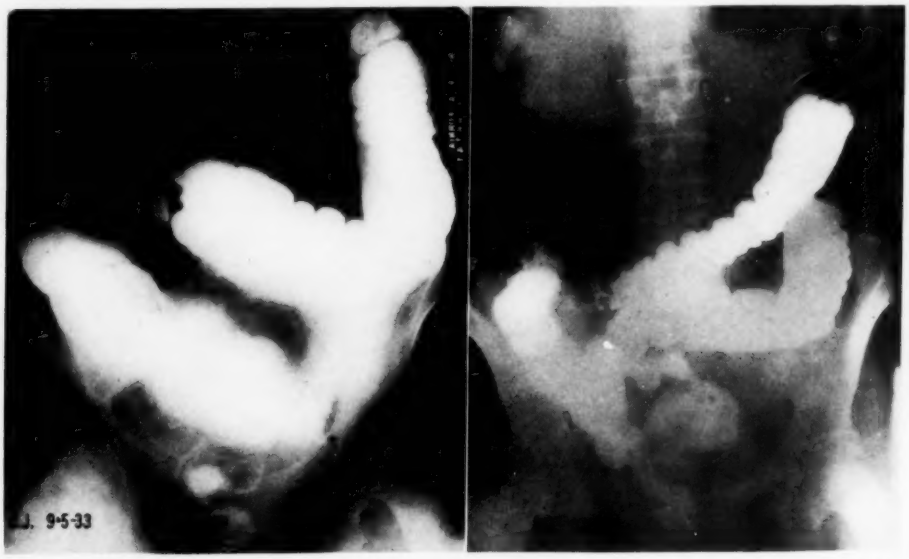

FIG. 4. Colon films taken after voluntary evacuation of the barium enema material. These show obvious increase in tone with resultant improved emptying.

barium was expelled, but after treatment there was a marked improvement in tone and much more of the barium could be expelled voluntarily. It is interesting to note that in spite of this demonstrable improvement in bowel function, there was practically no change in the patient's constipation. However, the bloating, gas, and upper abdominal pain of which she first complained had entirely disappeared after treatment was in progress. This improvement can perhaps be attributed to the increased tone of the small and large intestine. The symptoms leading up to her operation were prob-

ably of a functional nature and not connected with hypothyroidism. However, hypothyroidism as a cause of abdominal pain has been emphasized by Hinton [32] and Lisser.[24]

Anemia. Anemia of varying grades is found almost constantly in myxedema of any duration. It is usually secondary in type and in a certain percentage of instances will respond to thyroid medication alone, as in cases reported by Emery,[33] Mackenzie,[34] Stone,[35] and Lisser and Anderson.[13] In other cases, as pointed out by Lerman and Means,[36] iron is necessary in addition to the thyroid. The occasional similarity of the anemia to pernicious anemia, including the fairly frequent finding of achylia gastrica, has been noted by the above authors, but in the majority of the cases, the blood responds to thyroid, or, thyroid and iron. However, Means, Lerman and Castle,[37] and Lisser and Anderson,[13] have reported patients with coexistent myxedema and pernicious anemia, the latter diagnosis being supported not only by clinical and blood findings, but also by typical reticulocyte responses to liver therapy. In this group, of course, thyroid and liver therapy must be administered simultaneously.

When our patient was first seen, pernicious anemia was considered in the differential diagnosis, but the finding of normal acidity in the gastric juice made this diagnosis improbable. After treatment was started, thyroid alone was given for a period of two and one-half months. During the last two months of this period the metabolic rate was normal and there was marked improvement in most of the symptomatology, but the red blood cells and hemoglobin remained at practically the same level. The patient was then started on iron and ammonium citrate in addition to the thyroid. When she returned to the clinic after an interval of seven weeks, the blood picture had risen almost to normal. The counts were as follows:

	Hemoglobin (Sahli)	Red Blood Cells per cu. mm.
8–23–33	55 per cent	2,700,000
8–25–33	50 per cent	3,160,000
	Thyroid therapy started—	
10–23–33	55 per cent	2,810,000
11–20–33	45 per cent	2,800,000
	Iron and ammonium citrate started (in addition to thyroid)—	
1–16–34	76 per cent	4,660,000
2–16–34	80 per cent	4,450,000

This classifies the anemia as definitely of the secondary type, and one in which both iron and thyroid were necessary. It seems probable that the long duration of the anemia, as evidenced by the history of a blood test of "60" eight years before, was a factor in necessitating the administration of both iron and thyroid before improvement resulted. The results may also indicate that iron given routinely in conjunction with thyroid will probably result in the more rapid improvement of the secondary anemia of myxedema, even though it might eventually respond to thyroid alone. Such a conclusion was reached by Lerman and Means.[36]

Menorrhagia. The possibility of hypothyroidism as a cause for menorrhagia and metrorrhagia was noted by Salzman [38] and its frequency stressed by Lisser [39, 24] and Gardiner-Hill and Smith.[40] A striking case was reported by Lisser and Anderson,[13] and a recent article by Waters and Williams [41] contains an excellent review of the literature on this subject. The association is now widely accepted and it is, or should be, common practice to have a determination of the basal metabolic rate in patients where no obvious local pathology can be found to account for uterine bleeding. All authors agree that thyroid-therapy will reduce the bleeding to normal amounts if hypothyroidism is the etiologic factor.

The effect of thyroid-therapy on our patient's menses was marked and characteristic. Her menstrual history prior to treatment revealed that her periods had always been very profuse and lasted seven to eight days. During the year preceding entry they had been irregular, but continued to be profuse, lasting eight to ten days.

After therapy was started, the periods became regular, lasted three to four days, and there was a marked diminution in the amount of flow. This improvement has persisted.

Other Considerations. The presence of carotinemia can be explained partially by the patient's dietary habits, but it is obvious, as in most such cases, that normal people could eat a similar diet without developing the pigment retention necessary for increased icterus index and deposition of the pigment in the tissues. It seems logical to conclude that some metabolic change is partially, at least, responsible for the development of carotinemia. Since most patients with myxedema are described as having a yellowish tint, it would be interesting to see how frequently carotin can be detected in their blood serum. It may be that there is an increased incidence in myxedema similar to that noted by Rabinowitch [42] in diabetes, another disease of disturbed metabolism.

The depressed liver function, as evidenced by the definitely abnormal values in the Rose Bengal liver function test before treatment (specimen I—62 per cent retention; specimen II—44 per cent), is noteworthy, especially since hepatic dysfunction has been noted in hypothyroidism by Rowe [43] and Lisser.[24] The improvement after therapy to within approximately normal limits (I—53 per cent; II—32 per cent) apparently indicates that in this patient thyroid also had an effect on the rate of dye excretion through the liver. Retention was again found to be increased (I—78 per cent; II—60 per cent) after the operation, but how much of this was due to the lack of thyroid and how much due to the anesthetic is impossible to decide. The relation of the pigment retention of carotinemia to decreased liver function is another question for speculation.

Thyroid-therapy also influenced the sugar tolerance curve and the relatively flat curve before treatment was transformed into a curve somewhat similar to that seen in hyperthyroidism. After thyroid had been stopped the curve again became flat. The values are as follows:

Basal Metabolic Rate	Blood Sugar—Fasting	30 minutes	60 minutes	120 minutes
Minus 41%	77 mg. %	137 mg. %	156 mg. %	148 mg. %
Plus 3%	108 mg. %	186 mg. %	218 mg. %	141 mg. %
Minus 22%	82 mg. %	—	137 mg. %	84 mg. %

These results are somewhat similar to those published by Gardiner-Hill, Brett and Smith [44] in an article on this phase of myxedema.

Hypothyroidism vs. Myxedema. Cases of hypothyroidism without myxedema are not rare. King [45] noted that a low basal metabolism should be suspected in protracted menopause or chronic eczema. Lawrence [46, 47] noted thyroid failure without myxedema in patients whose chief complaints were headache and constipation. Higgins [48] reported similar cases and noted the occasional finding of edema. Blumgarten [49] stressed, in addition, rheumatoid pains and anemia. McKean,[50] Warfield,[51] and Hensel [52] note the frequency of this syndrome in the goiter region around the Great Lakes, but other authors, including Thurmon and Thompson,[53] Lisser and Anderson [13] and, more recently, Youmans and Riven [54] have reported groups of such cases from regions where goiter is not common. All report improvement of the various complaints on thyroid-therapy. The various manifestations have recently been catalogued by Lisser.[24]

Clinically our patient did not have typical myxedema, although she did present dry skin, pallor, and scanty, coarse hair. However, there was no puffiness of the features, she was not obese, and there were no subcutaneous fat pads. Her speech was slow but not otherwise remarkable and mentally she seemed alert. The picture was not one to be compared with that of Evans' patient [1] who presented typical far-advanced myxedema and on whom "the nurse made the diagnosis at one glance." It required some investigation before the diagnosis of hypothyroidism became apparent.

After considering the paucity of external signs, it is interesting to note the abundance of internal signs brought out by the clinical and laboratory investigations. The cardiac, intestinal, and bladder atony, as well as the anemia, were all typical of myxedema. Since the external signs were not at all typical, the term "internal myxedema" seems an appropriate designation for the findings in our patient. The presence of ascitic fluid makes this descriptive term even more pertinent.

Summary

A case of hypothyroidism is reported which showed ascites, cardiac, intestinal, and bladder atony, secondary anemia, menorrhagia and associated carotinemia.

The ascitic fluid was thought to be due to the hypothyroidism and showed a protein content above the average, but not as high as some previously reported.

The cardiac findings were typical of myxedema heart without decompensation.

The condition of bladder-atony is thought to be more common than previously reported.

The patient was followed over a period of 13 months and all symptoms and signs showed improvement on thyroid-therapy except the anemia, for the improvement of which iron was necessary in addition to the thyroid.

An exploratory laparotomy performed for symptoms simulating partial intestinal obstruction showed no evidence of other etiology for the ascites.

It is suggested that the term " internal myxedema " would best describe the findings in this patient.

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RECOVERY FROM CORONARY THROMBOSIS; REPORT OF EIGHT CASES, WITH PARTICULAR REFERENCE TO THE RECOGNITION OF THE LESS SEVERE AND ATYPICAL TYPES *

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Levine [1] in a study of 145 patients with coronary thrombosis found an immediate mortality of 53 per cent. Willius and Barnes [2] are also of the opinion that approximately 50 per cent die in the immediate attack. Conner and Holt [3] in studying a series of 287 patients with coronary occlusion found an immediate mortality of 16.2 per cent with a subsequent death rate of 55 per cent when averaged over a period of 3 months to 17 years. These statistical values are derived almost entirely from those patients who presented the classical clinical picture of coronary thrombosis and undoubtedly include principally those with the more severe grades of the disease. Little mention is made of those patients who have occlusions of the smaller coronary vessels and present atypical symptoms of less severity. Very few studies are available from which to estimate a mortality rate which includes this important group.

The diagnosis of thrombosis of the smaller coronary vessels is much more difficult than that of the classical attacks already so well described in the literature. The majority of patients having the less severe grades of the disease are usually diagnosed angina pectoris or "acute indigestion." Most often they are treated with nitroglycerine or with sodium bicarbonate and laxatives and allowed to continue the pursuit of their daily duties. In this group sudden death is frequent. Had a correct diagnosis been made of the nature of the initial attack, and the patient subjected to a period of four to six weeks of bed rest the fatal event might have been prevented or at least postponed.

It is the purpose of this paper to present five patients with the less severe grades of coronary thrombosis who did not manifest the ordinary clinical signs and symptoms of this disease. Without careful clinical and electrocardiographic studies these patients would have been diagnosed and treated as individuals with angina pectoris. Three patients with severe and unmistakable coronary occlusion are also reported because of their phenomenal recoveries and the serial electrocardiographic studies which they afforded.

The character of the pain is of great importance in diagnosing patients with atypical attacks of coronary thrombosis. A persistent substernal ache with substernal oppression is much more significant of coronary occlusion than is transient precordial pain. The possibility of unusual pain radiation, as has been pointed out by Libman [4] and others, must also be borne in mind.

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The pain may radiate to the mastoid regions, the shoulders, the elbows, and on some occasions to the abdomen. Occasionally the pain is felt in these remote areas without any conscious radiation from the sternum or left chest. In some instances pain may be entirely absent. Persistent substernal oppression may then be the significant symptom. The usual drop in blood pressure, increase in pulse rate, fever and leukocytosis are often absent in patients having the less severe forms of coronary occlusion. Then the only criterion by which a positive diagnosis may be reached is the demonstration of changes in the form of the T-wave * in electrocardiograms taken over a period of days or weeks.

The electrocardiogram of an individual is a remarkably constant curve unless altered by some pathological change in the myocardium or by the action of one of the digitalis bodies. The pathological events causing a sudden change in the structure of the myocardium are almost entirely limited to some disturbance in the blood supply of the myocardium. The most frequent cause of this is coronary thrombosis. Ischemia of the myocardium may occur as a sudden event and not be due to coronary vessel disease. This is probably best illustrated by large pericardial effusions. In this condition we sometimes see changes in the electrocardiogram similar to those that occur in coronary occlusion.[5] Katz and Wallace [6] have pointed out that myocardial ischemia may occur without coronary occlusion or pericardial effusion and produce changes in the electrocardiogram that may be confused with coronary occlusion. This occurred, however, only with advanced cardiac failure.

The demonstration of changes in the form of the T-wave occurring over a period of days or weeks in an individual who clinically suggests the possibility of coronary thrombosis is almost confirmatory evidence of this disease. This change may occur in the first few hours of the disease and disappear in even as short a time. Again it may not occur for several days and in some instances weeks after the accident has occurred.[6]

Individuals who have persistent substernal pain or recurring precordial pain of varying degrees of severity often do not show on one or two observations changes in the electrocardiogram suggestive of coronary thrombosis. If serial records are made over a period of several days, however, we can often demonstrate electrocardiographic changes strongly suggestive of small coronary infarctions. Should such changes be demonstrated the patient should be treated as one with a typical coronary thrombosis even though clinically he presents only the picture of an angina pectoris or less. Proger and Ayman [8] have shown that nitroglycerine may occasionally precipitate a dangerous lowering of blood pressure and that it should be used with great caution in treating paroxysms of pain in patients with hypertension or generalized vascular disease.

* Reference to the changes that occur in the T-waves includes also any changes that might occur in the S–T segments.

We believe that the early recognition and proper treatment of patients with the smaller and less severe occlusions will considerably reduce the mortality rate of this disease.

The following five case reports illustrate the diagnosis and recovery of patients with the less severe grades of coronary thrombosis.

Case Reports

Case 1. J. P., a 48 year old traveling salesman, was first seen in 1928 with an attack of renal colic. At this time the only complaint referable to the cardiovascular system was slight dyspnea on over-exertion. He had, however, experienced four attacks of "acute indigestion" with sharp pains in the epigastrium during the past four or five years. His blood pressure was at that time 120 mm. of mercury systolic and 70 mm. diastolic. There was no enlargement of the heart. The heart sounds were of normal quality. There was an early generalized arteriosclerosis.

Two years later the patient was seen complaining of a dull substernal ache on exertion. He also experienced a sense of oppression beneath the sternum. The blood pressure was 140 mm. systolic and 80 mm. diastolic. There was no significant change found on physical examination except an arrhythmia, due to premature auricular beats. The first sound at the apex was of fair quality and there was no enlargement of the heart. An electrocardiogram at that time (figure 1) showed evidence of myocardial disease but was not particularly suggestive of coronary disease. In the light of the previous attacks of epigastric pain associated with "indigestion" and the recent substernal oppression we suspected coronary disease and advised him to remain in bed for a period of at least four weeks. His symptoms rapidly subsided and at the end of this time he felt quite well and was allowed to return to part time work.

Comment. This patient did not at any time present symptoms sufficient to warrant a diagnosis of coronary thrombosis. The persistent substernal aching and sense of oppression were suggestive of coronary vessel disease and the changes that occurred between his first and second electrocardiogram made during an interval of one week justified a suspicion of coronary occlusion. The T-waves were inverted in all leads and associated with an S–T deviation from the base line. In the second record, seven days later, the T-waves were becoming upright. In the subsequent records made during the next 15 months the T-waves became completely upright in Leads I and II. We interpreted this change in the form of the electrocardiogram as indicating a small coronary occlusion, not sufficiently severe to produce clinical signs and symptoms of coronary thrombosis but involving enough of the myocardium to produce changes in the electrocardiogram.

Case 2. Mrs. W. S., a 47 year old housewife, was first seen on May 20, 1931, complaining of indigestion, precordial pain radiating down both arms, and nervousness. Three years before she first noticed palpitation and shortness of breath on exertion. One year ago she consulted a physician because of "indigestion." She was found at that time to have a blood pressure of 185 mm. systolic and 100 mm. diastolic. During the past two years she has had occasional attacks of substernal pain which radiated to the shoulders and down both arms. The attacks gradually became more frequent and severe. Any emotional upset or exercise would precipitate

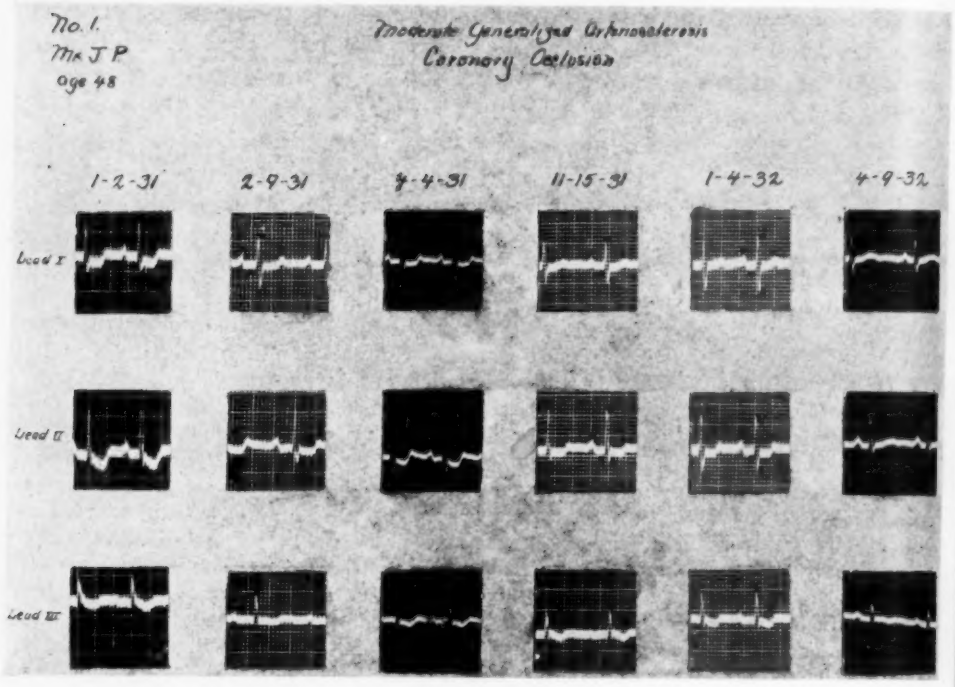

FIG. 1. J. P.

1–2–31. Substernal oppression and mild precordial pain first noticed a few days before this record was made. The T-waves are inverted in all leads. Slight depression of the S–T interval in Leads I and II. Slight elevation of the S–T take-off in Lead III.

2–9–31. After five weeks of rest in bed. Still notices occasional sense of oppression in the chest but no pain. The T-waves in all leads are tending to become upright.

4–4–31. Working as a traveling salesman. Notices only occasional twinge of precordial pain and some fullness in the epigastrium. The T-waves of Lead I have become upright.

11–15–31, 1–4–32, 4–9–32. Is symptom-free and working without difficulty. The T-waves of Leads I and II have finally become upright while the T-waves of Lead III are isoelectric.

an attack. The patient's family history was of interest in that she had a brother who experienced attacks of precordial pain and had an elevated blood pressure.

Physical examination showed a moderately obese, over-active, "high tension" woman of about 45 years. Her weight was 145 pounds. Her height was 63 inches. There was a moderate sclerosis of the temporal, radial and retinal vessels. There was a slight increase in the anteroposterior diameter of the chest. The heart was slightly enlarged. The first sound at the apex was of poor quality. The rate was 100 per minute. The rhythm was regular. The blood pressure was 165 mm. systolic and 95 mm. diastolic. Laboratory examinations gave normal results except for a questionable trace of sugar in the urine. There was some retention of tetradol in the gall-bladder dye test.

Because of the frequency and severity of the substernal pain the patient was admitted to the hospital. After two weeks of complete bed rest in the hospital the pain became less frequent and less severe. She was discharged to remain in bed at home for four or five weeks longer. At the end of this time the attacks of pain were much less and she was allowed light physical exercise. This was gradually increased

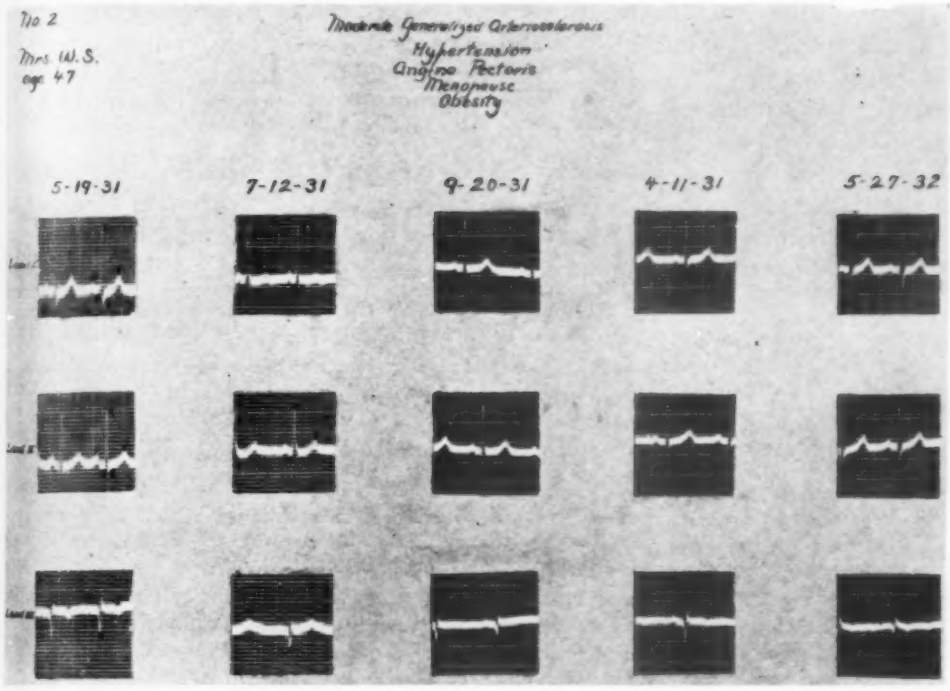

FIG. 2. Mrs. W. S.

5–19–31. Attacks of precordial pain on exertion or emotional upset for the past two years. More frequent and severe lately. In Lead III the "S" waves are deep and the T-waves are inverted.

7–12–31. After one month of bed rest the attacks of precordial pain have become less frequent. The T-waves of Lead I have become isoelectric and the T-waves of Lead III upright.

9–20–31, 4–11–31, 5–27–32. Moderate physical activity without discomfort. Very occasional attack of pain if emotionally upset or just preceding menses. The T-waves of Lead I have become upright and remained so throughout the remainder of the time she was observed. The T-waves of Lead III have again become inverted.

until she could, without discomfort, perform moderate physical exercise. There was an occasional recurrence of the attacks of precordial pain if the patient became emotionally upset and before the onset of her menstrual periods. The patient's weight was gradually reduced to her normal standard and her blood pressure gradually dropped from 165 mm. systolic and 95 mm. diastolic to 115 mm. systolic and 80 mm. diastolic.

Comment. This patient is quite typical of the individual usually labeled angina pectoris. Coronary thrombosis is seldom suspected until the fatal infarction occurs. The first electrocardiogram, made at the time of her admission to the hospital, showed no evidence of coronary infarction and very little evidence of myocardial disease. The second record, however, made after seven weeks of complete bed rest, showed very definite change in the form of the T-wave in Leads I and III. In Lead I the T-wave had definitely decreased its voltage and was almost biphasic. In Lead III the

T-wave which was inverted in the first record made, had become upright. No digitalis had been given at any time. Subsequent records made at irregular intervals during the next 10 months showed a return of the T-wave in Lead I to its upright position and the T-wave of Lead III once more became inverted.

These changes are difficult to interpret as a definite coronary thrombosis. The evidence, however, is strongly suggestive that some acute pathological changes occurred in the myocardium. This, in the light of the clinical history and physical examination, was probably associated with pathologic changes in the coronary vessels and it is difficult to conceive that a coronary spasm would be capable of producing such changes in the electrocardiogram over a period of 12 months. To treat such patients for coronary thrombosis is at least a safer procedure than to give nitroglycerine and allow them continued physical activity.

Case 3. Mrs. V. H., a 50 year old housewife, was admitted to the hospital July 6, 1931, complaining of pain over the lower part of the sternum which radiated up both sides of the neck. Five months before, while walking, she experienced a sensation of oppression in her chest and some precordial pain. This discomfort occurred only when she exercised, and disappeared on resting. During the past month the attacks of precordial pain have occurred almost every day and even while at rest. The radiation has extended down the left arm. She has also experienced considerable gas and fullness in the epigastrium after meals. The family history was of importance in that her mother died at the age of 60 with apoplexy.

On physical examination she was moderately obese. There was evidence of a moderate generalized arteriosclerosis and of slight cardiac hypertrophy. The blood pressure was 130 mm. systolic and 75 mm. diastolic. The heart sounds were of fair quality. There was a soft systolic murmur at the apex. There was slight tenderness in the epigastrium.

Laboratory examinations, which included a gastrointestinal series and gallbladder tests, showed nothing abnormal. A roentgen-ray of the lumbar spine showed a moderate hypertrophic arthritis.

During the five weeks' stay in the hospital the precordial pain became much less and she was generally improved. After leaving the hospital she remained in bed at home for four weeks. Light physical activity was then begun and gradually increased to moderate activity without difficulty. The attacks of precordial pain disappeared entirely and when last heard from seven months after her stay in the hospital she was complaining only of aching joints.

Comment. As in the preceding case report the clinical evidence of a coronary thrombosis is definitely lacking. The most obvious clinical diagnosis was angina pectoris. It is difficult, however, to conceive of such changes occurring in the electrocardiogram without definite pathological changes occurring in the myocardium. We are interpreting these changes in the T-wave and the S–T interval as evidence of a small coronary vessel thrombosis.

Case 4. Mrs. W. B. H., a 58 year old housewife, was first seen 10 years ago complaining of indigestion and nervousness. At that time she had slight dyspnea and

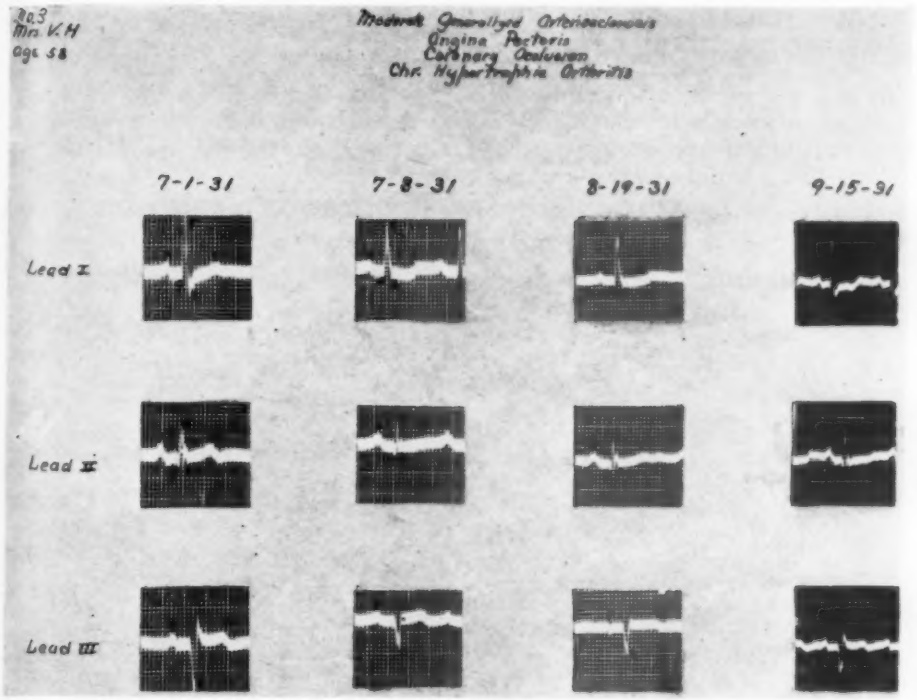

FIG. 3. Mrs. V. H.

7–1–31. Moderately severe attacks of precordial pain on exertion, and occasionally while resting, for several weeks. The S–T take-off is slightly below base line in Lead I and slightly below in Lead III.

7–8–31. After two days' complete bed rest, still having mild attacks of precordial pain. The T-waves of Lead I have become inverted and remained so during the remainder of our study. The T-waves of Lead II have decreased their voltage.

8–19–31. After about six weeks of bed rest attacks of pain are quite infrequent.

9–15–31. No more precordial pain. Complains only of pains in her joints.

palpitation of the heart on exertion. She also stated that for years she had experienced attacks of soreness in the upper left abdomen, usually after exertion.

Physical examination at this time showed a moderate generalized vascular disease. Her blood pressure was 140 mm. systolic and 90 mm. diastolic. The heart was slightly enlarged, measuring 10 cm. to the left. She was about 40 pounds overweight. Her blood and urine examinations at this time were normal. A gastrointestinal series showed nothing unusual.

February 11, 1932, ten years after her first visit, she consulted us complaining of a dull substernal pain with radiation to both mastoid regions. This had occurred one week before while climbing a flight of stairs. The substernal pain lasted intermittently for two or three days and then disappeared to return again two days later. It was intermittently present from then until her office visit. It was made worse by physical exercise or emotional upsets.

On examination she was obese. There was moderate general vascular disease. The heart was slightly enlarged. The heart rate was 74 and the rhythm was regular. The sounds were of fair quality. There were no significant murmurs. The blood pressure was 150 mm. systolic and 90 mm. diastolic. There was no evidence of circulatory incompetence. The temperature was normal and she was in no great discomfort.

An electrocardiogram made at this time (figure 4) showed evidence of definite myocardial disease but was not particularly suggestive of a coronary lesion.

We advised a prolonged period of bed rest and this was carried out for six weeks. The pain and substernal discomfort became considerably less, occurring only at infrequent intervals when emotionally disturbed. At the end of six weeks she was allowed light physical activity and this was gradually increased to moderate physical

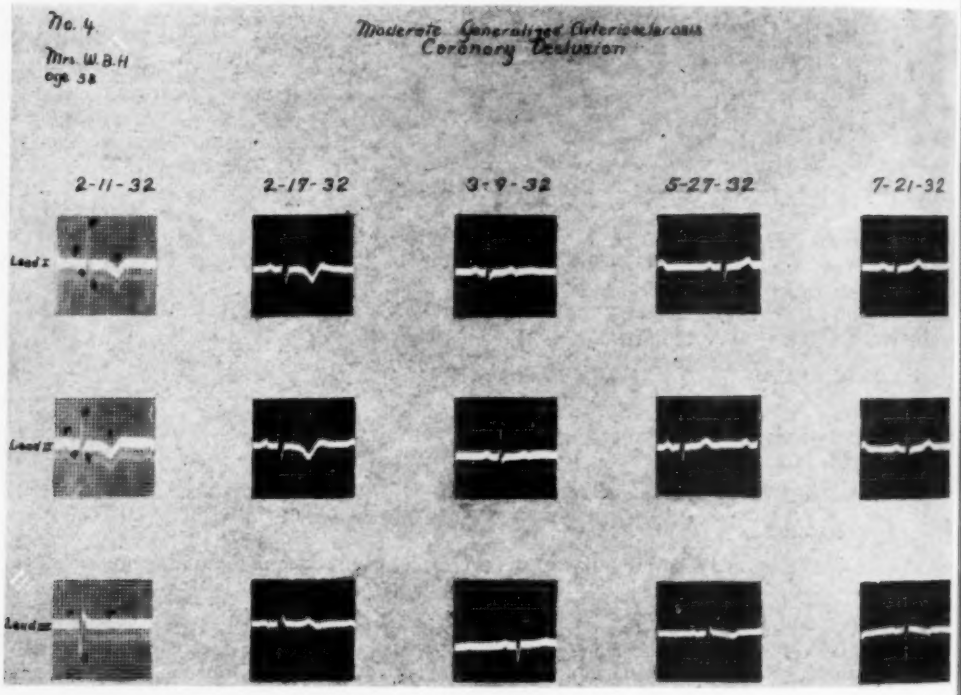

FIG. 4. Mrs. W. B. H.

2–11–32. Two days after experiencing substernal oppression and aching while walking up steps. No actual precordial pain. No definite clinical evidence of a coronary occlusion. The T-waves of Leads I and II show sharp inversion.

2–17–32. After six days' bed rest slight substernal aching and oppression are still experienced. The sharply inverted T-waves of Leads I and II are unchanged.

3–9–32. After one month of bed rest. Substernal oppression experienced occasionally if emotionally upset. The T-waves of Leads I and II are becoming upright.

5–27–32, 7–21–32. The patient is capable of light physical exercise without discomfort. Occasional attack of mild substernal oppression. The T-waves of Leads I and II have become completely upright. In Lead III they have become inverted. There is very little evidence of pathology in these last records.

activity which she could perform without great difficulty. She still occasionally complains of substernal discomfort if emotionally upset or if she undertakes more than moderate physical exercise. During the period of bed rest there were no essential changes in blood pressure or elevation of temperature, and no leukocytosis.

Comment. An electrocardiogram made after one week of bed rest was almost identical with the first record. A third electrocardiogram made after four weeks of bed rest showed a change in the form of T-waves in

Leads I and II. The sharp inversion in Leads I and II was beginning to become upright. Subsequent records made at intervals of three and five months after the first observation showed a complete return of the T-waves in Leads I and II to their normal upright position. The T-wave in Lead III became inverted but otherwise the record appeared perfectly normal.

Here again the clinical evidence of coronary thrombosis was lacking. A consideration of this patient's clinical course, together with the changes that occurred in her electrocardiogram over a period of four weeks, makes one suspect strongly an occlusion of a coronary vessel, which did not present typical signs and symptoms of this disease.

Case 5. Mr. C. C., a hard working, high tensioned, traveling salesman of 50 years, was first seen in the office one week after having been seized with a moderately severe attack of pain in the left chest while driving his car. He stopped at the next town and consulted a physician who gave him some tablets which relieved his pain.

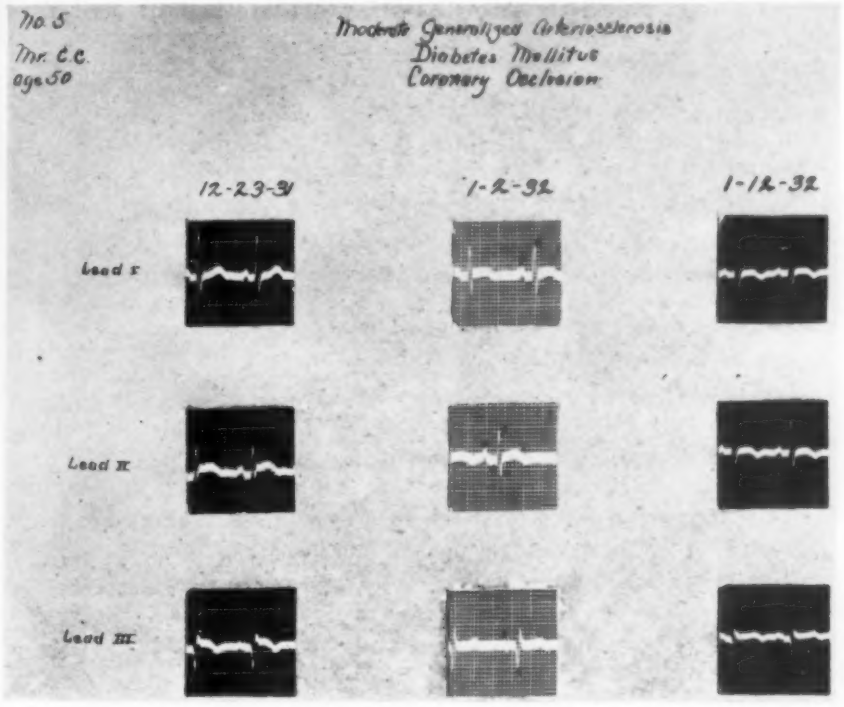

FIG. 5. Mr. C. C.

12-23-31. Three days after several attacks of precordial pain of moderate severity. Slight elevation of the S–T interval in Leads II and III. The T-waves of Lead III are inverted.

1-2-32. After 10 days of complete bed rest. No further precordial pain. The T-waves of Lead I have decreased their voltage. The T-waves of Lead III have become upright.

1-12-32. After three weeks of bed rest. The T-waves of Leads I and II have become definitely inverted. The S–T interval in Leads I and II has become dome shaped. Over our protest the patient resumed his duties as a traveling salesman and has had no further precordial pain.

He continued his trip but that night there was a recurrence of the pain. The following day he felt quite well. Four days later he again experienced a constant, dull, non-radiating pain in the precordial region. He consulted another physician who told him that he had diabetes mellitus and neuritis. He visited our office one week after the initial precordial pain.

Physical examination at this time showed the patient to be in no great discomfort. He was of the short, stocky, plethoric type. There was a moderately advanced arteriosclerosis of the peripheral vessels. The tonsils were chronically infected. Chest examination was not abnormal. The apex impulse of the heart was not visible or palpable. The heart was not enlarged. The first sound at the apex was distant. There was a short, soft systolic blow. The heart rate was 100 per minute. The rhythm was regular. The blood pressure was 115 mm. systolic and 70 mm. diastolic. There was no edema, cyanosis or any other evidence of circulatory failure. His temperature was 100.4° F.

A leukocyte count was 10,000 with 74 per cent polymorphonuclears. Examination of the urine was positive for sugar, acetone and diacetic acid. A fasting blood sugar was 175 mg. per 100 c.c. An electrocardiogram showed an elevation of the S–T segment in Leads II and III, an inversion of the T-wave in Lead III and a prominent Q_3. The patient was advised a period of complete bed rest, a diet was outlined and 10 units of insulin were given twice daily. No more attacks of precordial pain were experienced after going to bed. In a second electrocardiogram made one week later the T-waves in Lead III had become upright and in Lead II it was becoming biphasic. A third electrocardiogram made three weeks after the onset showed inversion to have occurred in T_1 and T_2 with some rounding of the S–T segment in these leads. After three weeks of bed rest the patient then insisted upon taking up his duties as a traveling salesman. Two years have elapsed since this time and there has been no recurrence of the precordial or substernal discomfort.

The patient has not been seen since the last electrocardiogram was made but inquiries reveal that he is carrying on his usual work without discomfort.

Comment. This patient is one of the group that is often classified as angina pectoris. He also illustrates the not infrequent association of coronary disease and diabetes mellitus. His coronary thrombosis in all probability involved only a small vessel as there were very few of the usual signs of this disease.

The following three cases presented no diagnostic difficulties; the clinical features of coronary thrombosis were such as could be diagnosed even without the aid of the electrocardiogram. They are reported because of their interesting recoveries and the data afforded by the serial electrocardiograms. They illustrate the recovery of patients with the more severe lesions and their return to a moderate degree of usefulness.

Case 6. Mr. H. B., a rather high tensioned business man of 57 years who had been a known hypertensive for five years, was first seen at home on January 29, 1932. The day before, while having some dental work done, he first noticed slight substernal pain. A few hours later the substernal pain became more excruciating. He was nauseated and vomited. Shortly after vomiting, the pain subsided and he was comfortable for several hours. About two o'clock the next morning he was awakened with excruciating precordial pain, substernal oppression and breathlessness.

On physical examination at this time he was pale and cyanotic. His respirations were of the Cheyne-Stokes type and his blood pressure had dropped from its usual level of 190 mm. systolic and 100 mm. diastolic to 100 mm. systolic and 70 mm.

diastolic. The heart was slightly enlarged. The sounds were distant and there was a light pericardial friction rub. The heart rate was 120 and the rhythm grossly irregular. A leukocyte count was 18,600 with 80 per cent polymorphonuclear leukocytes.

For the next 10 days the patient's clinical course was quite stormy. Hiccoughs and abdominal distention were very severe. Auricular fibrillation was paroxysmal and for several days the degree of circulatory shock was marked. His temperature elevation fluctuated from 99 to 101 degrees for one week. After 10 days the patient's general condition was considerably improved and after remaining in the hospital for four weeks he was transferred home to remain in bed for six more weeks. Ten

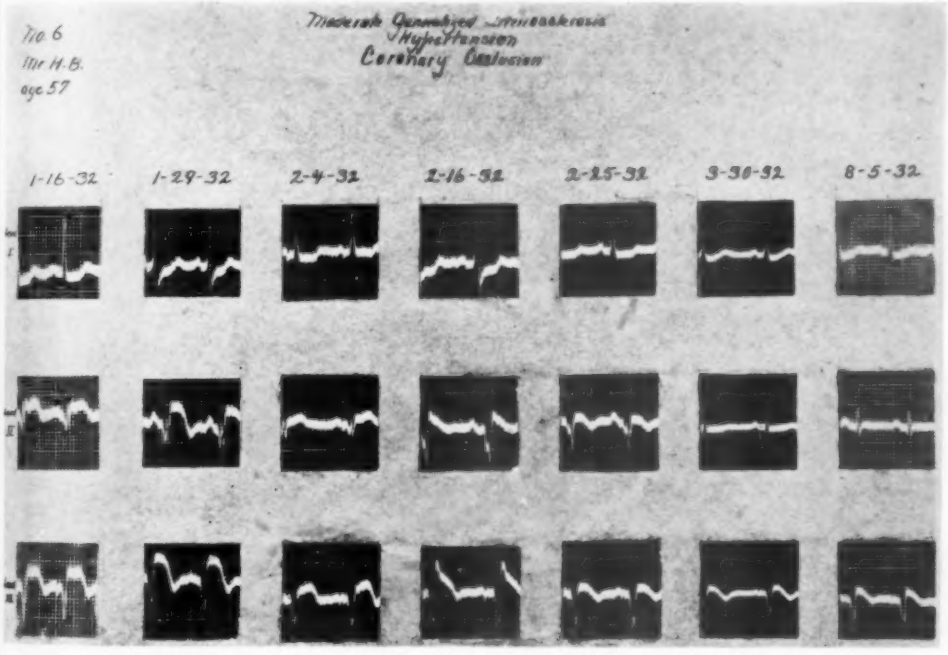

FIG. 6. Mr. H. B.

1–16–32. Eight hours after a severe coronary occlusion. The S–T interval of Leads II and III shows a marked elevation of the S–T take-off.

The subsequent records show the successive changes that occurred in the T-waves as healing progressed. At present he is capable of performing moderate exercise.

weeks after the occlusion light physical activity was first begun. This was gradually increased during the next four months and since then he has been able to participate in moderate physical activities. His blood pressure has remained at a lowered level of around 130 mm. systolic and 90 mm. diastolic. The heart rhythm is regular except for occasional ventricular premature beats. For several months after the occlusion the patient would experience rather frequent attacks of substernal oppression and soreness. This has gradually decreased and at the present time he experiences only occasional sensations of palpitation with the ventricular premature beats. Nine months after the coronary accident the patient had influenza and pneumonia. No cardiac complications occurred during this illness and his recovery was uneventful. Two years have now elapsed since the coronary occlusion. He is

capable of performing moderate physical exercise and he seldom experiences any symptoms referable to the heart.*

Comment. This patient illustrates the more severe grade of coronary thrombosis. The complication of auricular fibrillation presented a problem in therapy as to whether or not digitalis should be used. To leave the ventricular rate extremely rapid and its rhythm irregular, or to risk the possible dangers of digitalis effect on the infarcted myocardium was the question. We elected to use digitalis in an effort to control the heart rate. There were no untoward results from this and as healing began the auricular fibrillation spontaneously disappeared. The patient also presented intractable hiccough. This too disappeared spontaneously.

The first electrocardiogram made about eight hours after the initial coronary occlusion showed a depression of the S–T interval in Lead I and a marked elevation of the S–T interval in Leads II and III. The second record made three days later showed an exaggeration of these findings. A record made 19 days after the thrombosis had occurred showed a beginning return of the S–T take-off to the base line. During the subsequent months an inversion of the T-wave in Leads II and III occurred and the S–T take-off gradually returned toward the base line.

Even though this patient's infarcted area was very extensive his recovery has been quite satisfactory and he is now capable of performing moderate physical activity.

Case 7. Dr. J. T., a 45 year old, strenuous, hard working practitioner, was first seen June 16, 1931. He had been a known hypertensive for 20 years. Three days before, while driving some stakes in his back yard, he experienced pain in both elbows. The next day while driving his car he was seized with a moderately severe precordial pain. He stopped for a few minutes and the pain became less. A few hours later he consulted us in the office.

On examination at this time the patient was in no great discomfort. There was no evidence of circulatory failure or cyanosis. There were moderate generalized vascular changes. The heart was slightly enlarged. The first sound at the apex was of good quality. No murmurs were heard. His blood pressure was 150 mm. systolic and 90 mm. diastolic. He stated that his average blood pressure was around 180 mm. systolic and 100 mm. diastolic. The heart rate was 90, and the rhythm was regular. His temperature was 99 degrees. He was about 40 pounds overweight.

An electrocardiogram made at this time showed a very low voltage and inverted T-wave in Lead I. The T-wave in Lead II was also of low voltage and biphasic. There was a left axis deviation.

The patient was advised to go to bed at once. Instead he went to a hospital and performed a laparotomy. Shortly after this he collapsed with acute precordial pain. He was seen a few hours later at home acutely ill with moderate circulatory collapse. His blood pressure had dropped to 115 mm. systolic and 70 mm. diastolic. The heart rate was 130 and his rhythm was regular. The heart sounds were quite indistinct. The temperature was 101 degrees. A leukocyte count was 14,600 with 68 per cent polymorphonuclear leukocytes. Examination of the urine showed nothing abnormal.

For the following two weeks the patient was quite ill. A pericardial friction rub was heard 48 hours after the acute occlusion. The temperature elevation continued

* This patient died of congestive heart failure in May 1934, twenty-nine months after his coronary thrombosis.

from 100 to 101 degrees for 10 days. After this time the precordial pain subsided. The convalescence was uneventful. He remained in bed for eight weeks and then for a period of two weeks he participated in light physical activities. Ten weeks after the acute occlusion the patient resumed his practice and since that time he has had only very occasional slight attacks of substernal discomfort. Two and one-half years have now elapsed since the coronary thrombosis and he still feels quite well. In spite of our warning he is working quite as hard as he did before the coronary accident.

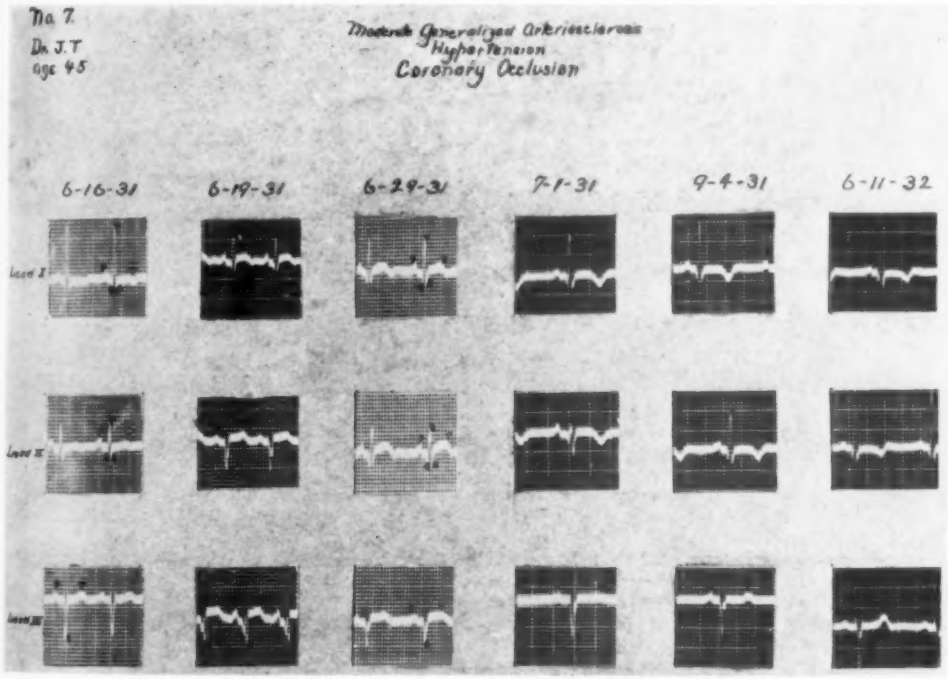

FIG. 7. Dr. J. T.

6–16–31. Forty-eight hours after a mild attack of precordial pain. The T-waves of Lead I are inverted and the T-waves of Lead II are biphasic.

6–19–31. Twenty-four hours after a second and very severe attack of precordial pain. Clinically he then presented a typical picture of coronary occlusion.

The subsequent records show the changes that occurred in the T-waves and the S–T intervals during the process of healing. On 6–11–32 he was performing his duties as a general practitioner without difficulty.

Comment. From the clinical course it seems that this patient's coronary thrombosis began about 72 hours before his final collapse. It is not improbable to suppose that it began either as a partial occlusion of one of the larger vessels or a complete occlusion of one of the smaller vessels. With continued physical activity the thrombosis became more extensive until it completely shut off one of the larger vessels. Then circulatory collapse ensued. It is of interest to speculate as to whether or not the lesion would have progressed to the severe grade had the patient gone to bed at the time his first symptoms were manifested.

The electrocardiograms taken over a period of one year after the acute occlusion show interesting changes. The record made before the coronary occlusion became complete showed only a slight inversion of the T-wave in Lead I. Three days later, and about four hours after the occlusion became complete, an elevation of the S–T take-off in Leads I and III was first detected. There was also a considerable increase in the shattering of Q–R–S. Two weeks after the complete occlusion the S–T interval was still elevated in its take-off and was beginning to assume the dome shape seen in healing coronary occlusion. Subsequent records made during the next 11 months show the T-waves assuming a sharp inversion in Leads I and II and a return of S–T take-off to its isoelectric level.

This patient again illustrates that the infarcted area can be quite extensive and the patient still recover sufficiently to engage in a useful occupation.

Case 8. Mr. T. S., a 63 year old night watchman, was seen first at 2 a.m., January 6, 1932. A few minutes before, while walking up a flight of stairs, he had been suddenly seized with excruciating pain in the left chest and behind the sternum. When seen he was in a rather advanced state of shock. His color was ashen, perspiration was profuse and the radial pulses were weak and thready. His blood pressure was 80 mm. systolic and 60 mm. diastolic. His heart rate was 120 and regular. There was moderately generalized vascular sclerosis. The heart was not definitely enlarged. The first sound at the apex was quite distant and of poor quality. There was no evidence of pulmonary congestion and the liver was not felt.

The patient was immediately hospitalized. Morphine in one-half grain doses was given and repeated at three hour intervals in order to control the pain.

His "post-thrombosis" course was quite stormy. The temperature ranged from 100 to 101°, his heart rate from 100 to 120 and he had considerable abdominal distention. He had some hiccough and in spite of large doses of morphine his pain persisted for two or three days.

After three or four days his general condition improved. His blood pressure increased to 120 mm. systolic and 90 mm. diastolic. The pain disappeared and his recovery was uneventful. He remained in bed two months. Since then he has gradually increased his exercise until at the present time he is capable of performing light work without discomfort.

Comment. An electrocardiogram made 10 hours after the coronary thrombosis shows very little evidence of the accident. This illustrates well that even with an extensive coronary occlusion the changes in the electrocardiogram may not be demonstrable for several hours or even days after the occlusion. In the electrocardiogram made three days after the occlusion only an inversion of the T-wave in Lead III had occurred. Subsequent records made at intervals of three weeks and six months showed an inversion of the T-wave in Leads I and II.

Even though this patient had a moderately advanced generalized vascular disease and an extensive coronary occlusion his recovery has been rather complete in that he does not experience any symptoms referable to the heart even when performing light physical exercise.

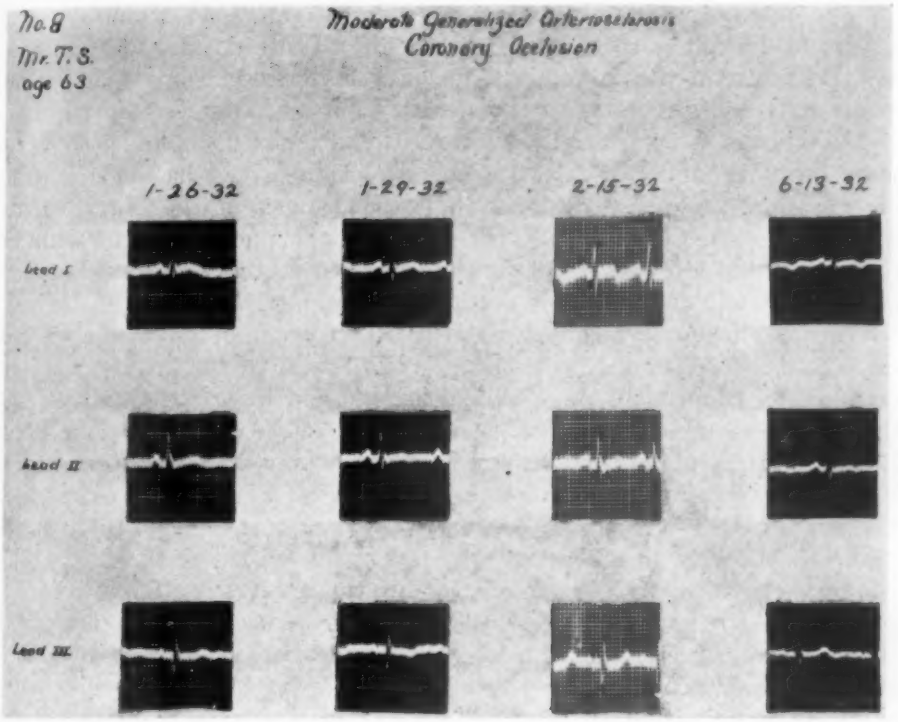

FIG. 8. T. S.

1–26–32. Twenty-four hours after an attack of prostrating precordial pain. The T-waves show no evidence of coronary occlusion. Q- and U-waves in Lead III are suggestive of coronary occlusion. Clinically the patient had a typical attack of coronary occlusion.

1–29–32. Four days after the onset. The T-waves of Lead III have become inverted. The T-waves of Leads I and II still show no evidence of occlusion.

2–15–32. Twenty days after the occlusion. The S–T interval of Lead I has become definitely dome shaped and the T-waves of Lead I have become inverted. The T-waves of Lead II have become upright.

6–13–32. About six months after the coronary occlusion the T-waves in Lead I remain inverted. The patient can perform moderate physical activity without discomfort.

GENERAL DISCUSSION

Death from coronary thrombosis is usually caused by ventricular fibrillation, a rupture of the infarcted area or the throwing off of an embolus. Complete rest offers the best possibility of avoiding these complications. An early diagnosis and the strict enforcement of complete rest are probably the most important factors in the treatment of this disease. The first 21 days after coronary thrombosis constitute the critical period of this illness. If this is passed without complications healing will usually take place and the infarcted area will begin to fibrose. If the infarcted area is not too extensive the heart muscle will remain perfectly competent. As sequelae of large healed infarctions, cardiac hypertrophy and failure sometimes occur during the subsequent months.

The diagnosis of the more severe grades of coronary thrombosis is as a rule not difficult as they usually present the classical syndrome already so well described in the literature. The less severe occlusions that do not manifest typical symptoms of this disease offer an extremely evasive diagnostic problem. They are most frequently diagnosed angina pectoris or some intra-abdominal disease. A correct diagnosis can be made only by the electrocardiographic demonstration of changes in the form of the T-wave in successive records. This diagnostic change may occur within a few hours or not for several days. One or two normal electrocardiograms are consequently of no value in excluding a coronary occlusion.

In order properly to evaluate changes that occur in successive electrocardiograms the technic of making the record must be faultless. Artefacts from faulty connections, high skin resistance and loose strings may cause error to creep into our interpretation. The effect of digitalis or one of its allies must be borne in mind as a factor that may alter the form of the T-wave. Excluding technical error and the effect of drugs, any change in the form of the T-wave of a " coronary suspect " must be regarded as indicative of a coronary thrombosis.

Once the diagnosis is established treatment resolves itself into complete rest for six to eight weeks. Morphine should be used liberally to control the pain and insure complete quiet. Inhalations of oxygen by nasal catheter should be given continuously during the shock stage. Metaphyllin in 0.3 gram doses intravenously is also of value in relieving the pain of the immediate attack.[9] It may also increase the coronary blood flow and accelerate healing when given by mouth three times daily in 1.5 grain doses. Levine[9] has suggested the prophylactic use of quinidine sulphate in doses of 4.5 grains three times a day during the 21 day critical period after coronary thrombosis in order to prevent the possibility of ventricular fibrillation. Digitalis is of no value unless cardiac failure or auricular fibrillation is a complication.

After the six to eight week period of bed rest convalescence should be very gradual. The patient should be reëducated as to his mode of living and his occupation. Avoidance of unnecessary physical or mental strains is an essential.

If an electrocardiogram is not available it is much the wiser plan to treat a patient with angina pectoris as one with coronary thrombosis than to treat one with coronary thrombosis as angina pectoris.

Through voluminous publications on this subject the medical profession is quite well instructed as to the diagnosis and treatment of the usual patient with coronary thrombosis. The purpose of this paper is to call attention to those patients who have a thrombosis of the smaller coronary vessels and who do not present the usual classical signs and symptoms of this disease. By the proper diagnosis and treatment of this group we believe the mortality of this disease may be reduced.

Summary

1. We have presented eight patients who have recovered from coronary thrombosis.

2. Five of these did not manifest the usual clinical signs and symptoms of coronary thrombosis and ordinarily would have been diagnosed angina pectoris.

3. By careful clinical study and serial electrocardiographic tracings taken over a period of days or weeks the diagnosis of coronary thrombosis was established in these patients not presenting the typical signs and symptoms.

4. We believe that the immediate mortality from coronary thrombosis may be materially reduced by the early diagnosis and treatment of patients who fail to manifest the usual signs and symptoms of this disease.

Follow-Up Note

No deaths have yet occurred in the first five patients having the milder attacks of coronary occlusion. From 33 to 46 months have elapsed since their initial attacks. A second attack occurred in one (case 1) 25 months after the first attack. He made an uneventful recovery from this and is now working and without symptoms. All other patients in this group are capable of carrying on their daily duties.

Of the three patients having the severe coronary occlusions, one (case 6) died 29 months after the initial attack with congestive heart failure. Another (case 8) is living and is in fair health, and the third patient (case 7) is without symptoms and doing a large general medical practice 40 months after the initial attack.

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CASE REPORTS

PULMONARY TORULOSIS: REPORT OF A CASE *

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SYSTEMIC infections due to *Torula histolytica* are uncommon, a total of 45 authentic cases having been collected from the literature up to 1934, by Johns and Attaway.[1] These authors added one case of their own. Thirty-one cases occurred in the United States. The fact that 36 cases have been reported in the past decade is a probable indication that fewer cases are going unrecognized than formerly. Previous to publication of the monograph of Stoddard and Cutler[2] classification of the pathogenic yeasts was based on incomplete data and the medical nomenclature of infections produced by them was in a state of confusion. At present there are available many criteria [2, 3, 4, 5] for the identification of torula, and differentiation of torulosis from oidiomycosis. Sheppe [4] defines torula as a yeast which multiplies by budding, does not produce ascospores, does not ferment carbohydrates and does not produce a mycelium in tissue or on culture. Oidium he defines as a yeast which multiplies by budding, does not produce ascospores, does ferment carbohydrates and does produce a mycelium when growing on culture. Rappaport and Kaplan [5] were the first to report immunologic reactions, as determined by agglutination, absorption and complement fixation tests, in experimental animals (rabbits and guinea pigs), which had been immunized against *Torula histolytica* and against two strains of oidium. While widespread systemic infection with torula may occur, it is generally considered [1, 2, 3, 4, 6] that this organism shows a special tendency to invade the meninges. Of 18 cases tabulated by Stone and Sturdivant [3] in 1929, the central nervous system was chiefly involved in 15. The portal of entry is considered to be the respiratory tract.[3, 4, 5, 6] Torula is widely distributed in nature, having been cultivated from wasp-nests, many grasses, plants and trees, fruits, bees, insects, canned butter, milk, pickle-brine, and soil. While several instances of pulmonary involvement have been reported as part of a systemic infection or accompanying a torula meningitis [2, 3, 5] cases in which the lesions are limited chiefly or entirely to the lungs are exceedingly rare. Sheppe [4] reported a case confirmed by necropsy, in which the right lung showed an organizing bronchopneumonia. There was no evidence of involvement of the central nervous system. Torula was obtained from the pulmonary lesions, grown in pure culture, and reproduced the disease by animal inoculation. Berghausen,[7] in 1927 reported a case in which torula was isolated from an ulcer on the tongue, and in which both lungs showed infiltration not typical of tuberculosis. This case also terminated fatally; necropsy was refused. McGehee and Michelson [8] report a case of inguinal abscess in a negro, due to torula infection, with recovery.

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Freeman,[6] reviewing the literature in 1931, collected 42 cases and added one of his own. He observed that evidences of involvement in other parts of the body (than the central nervous system) are rare; that occasionally a lesion may be found in one lung, and more rarely a general infection, indicated by obtaining the torula in pure culture from the blood and urine. According to this author, lesions in the lungs may be either acute or chronic.

The pathology in the lungs [3, 4, 5, 7, 9] is described as either a consolidation, or scattered nodules; there may be abscess formation. In the case reported by Stone and Sturdivant [3] the consolidated portion of the lung had a circumscribed and well-defined outline, was firm in consistency and of grayish-white granular appearance, resembling a tumor. In another case [4] the consolidated lung was dark brown in color; the consolidation was not as definite as that noted in lobar pneumonia at the stage of gray hepatization. Little or no tendency to pleural involvement has been reported.

Hirsch and Coleman [9] report a case of acute miliary torulosis of the lungs, associated with torula meningitis. In a fourth case, reported by Berghausen,[7] not confirmed by necropsy, but in which torula was isolated from an associated ulceration on the tongue, stereoscopic films of the chest showed diffuse bilateral infiltration of the lungs; the apices were apparently clear.

The case reported by Sheppe [4] is unique in that the lesions were localized in the lung, with no evidence of invasion of other organs or systems by the fungus. This author states that the clinical findings were those of a moderate toxemia, with slight fever and leukocytosis, and that in diagnosis pulmonary syphilis, lung abscess or tuberculosis may be suspected. In the case observed by Rappaport and Kaplan [5] nodules due to torulosis were found in the lower lobe of the right lung, with fibrocaseous tuberculous involvement of the upper lobe.

The prognosis, in cases with involvement of the central nervous system, is hopeless. All such cases collected from the literature by Stone and Sturdivant [3] terminated fatally. Sheppe [4] believes that pulmonary cases tend to recovery. No form of treatment has been proved to have any value. Iodides have been extensively used, also tartar emetic. Other drugs unsuccessfully employed include hexamethylenamine and gold sodium thiosulphate, intravenously.[3] A torula vaccine has been injected intravenously.[10]

The following case is reported as one of localized pulmonary torulosis presenting roentgenographic evidence of lesions quite distinct from those of a pre-existing pulmonary tuberculosis.

Case Report

History. On February 14, 1933, P. R. G., white male, aged 33, was admitted to Fitzsimons General Hospital. The family history was irrelevant. Three years before admission he had had a roentgen-ray film of the chest made because of a severe upper respiratory infection (figure 1). This showed some infiltration, chiefly of left upper lobe. He remained at his duties until January 1933, although for the preceding three months he had had cough and expectoration.

Examination. The patient was ambulant, afebrile, and not apparently seriously ill. General nutrition was good. The chest showed diminished resonance over the left upper with parenchymal râles; râles were heard also over the right mid-chest, anteriorly, and at angle of the right scapula, posteriorly. The blood pressure was 100 mm. Hg systolic and 75 diastolic.

Laboratory Findings. A roentgenogram of the chest showed nodose involvement, most marked in the left upper, the right mid-lung and the right base. The lesions in the right lung had a radial distribution not typical of tuberculosis (figure 2). Sputum examinations, including animal inoculation, were negative for acid fast

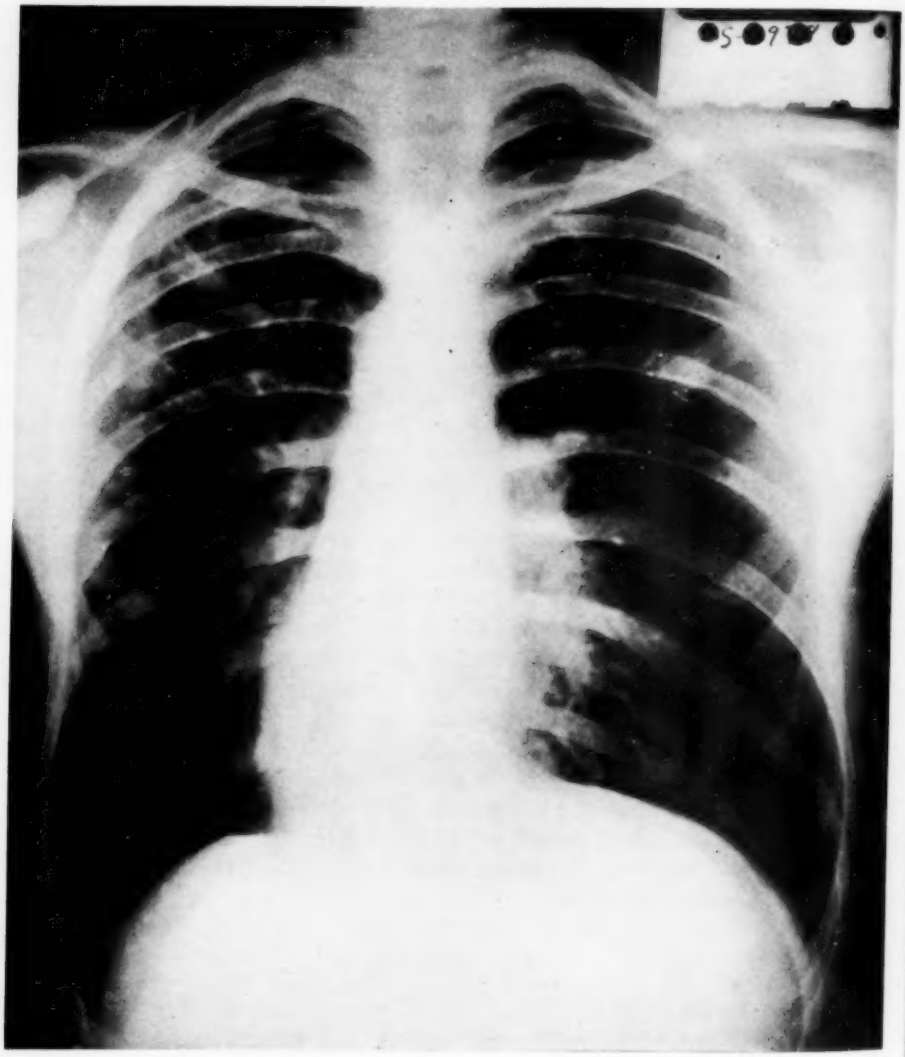

FIG. 1. Roentgenogram of chest, May 20, 1930.

bacilli. Yeast buds were found in direct smears and in cultures of the sputum, and were also found in smear and culture of material from bronchoscopic aspiration. Bronchoscopy showed moderate congestion of the bronchial mucosa; no free secretion was noted. This yeast was identified as *Torula histolytica*. It showed on culture a spherical budding yeast of medium size. It did not form spores on plaster blocks,

carrot agar or Gorodkova's agar. No sugars were fermented. It was highly virulent for white mice, killing in two or three days with a generalized peritonitis. The blood Wassermann and Kahn tests were negative. Spinal puncture: fluid clear,

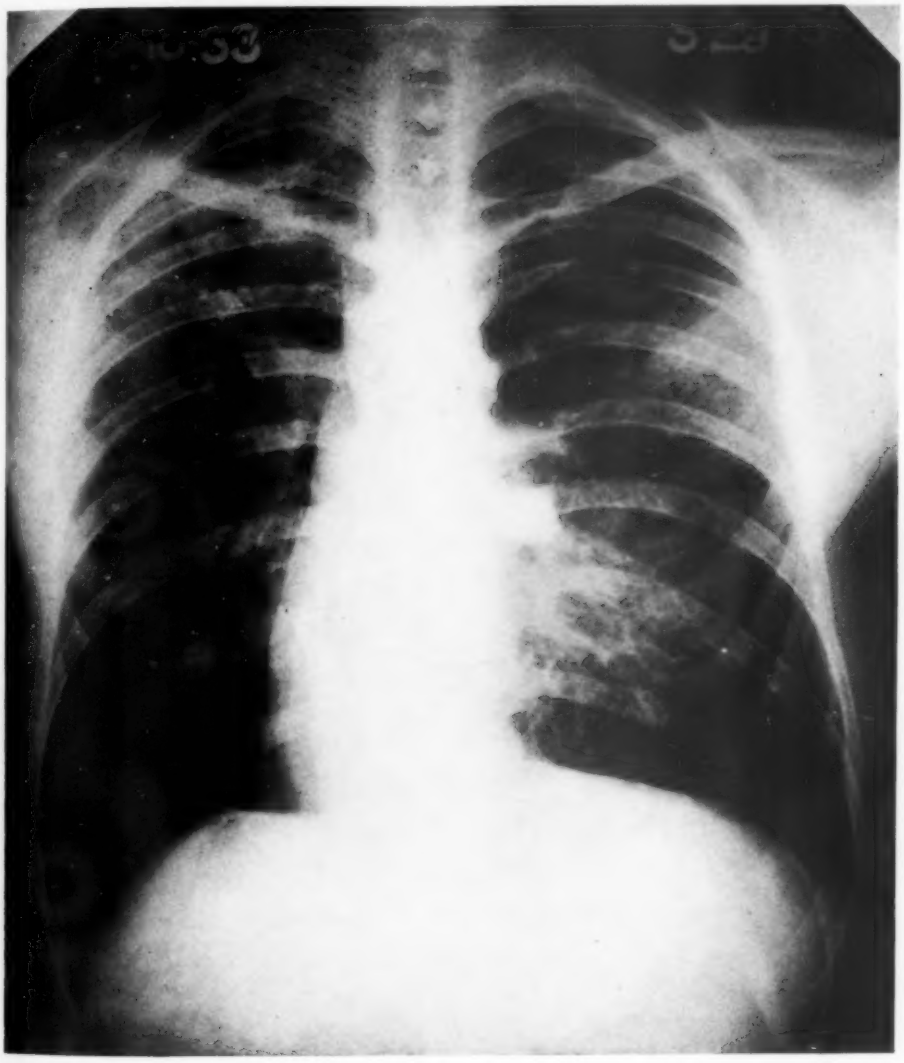

FIG. 2. Roentgenogram of chest, February 18, 1933.

pressure normal, cell count 6, sugar normal, globulin no increase; smear and culture showed no fungi.

Course of the Disease. This was uneventful. The patient remained under observation for 15 months. During this time the pulmonary lesions showed very little change (figures 3 and 4). He remained afebrile, his weight was stationary and he

had practically no subjective symptoms. He was discharged April 30, 1934 feeling well, with slight cough and expectoration. On physical examination at discharge, râles over both sides of the chest were still heard unchanged. The patient was still feeling well when last heard from in November 1934.

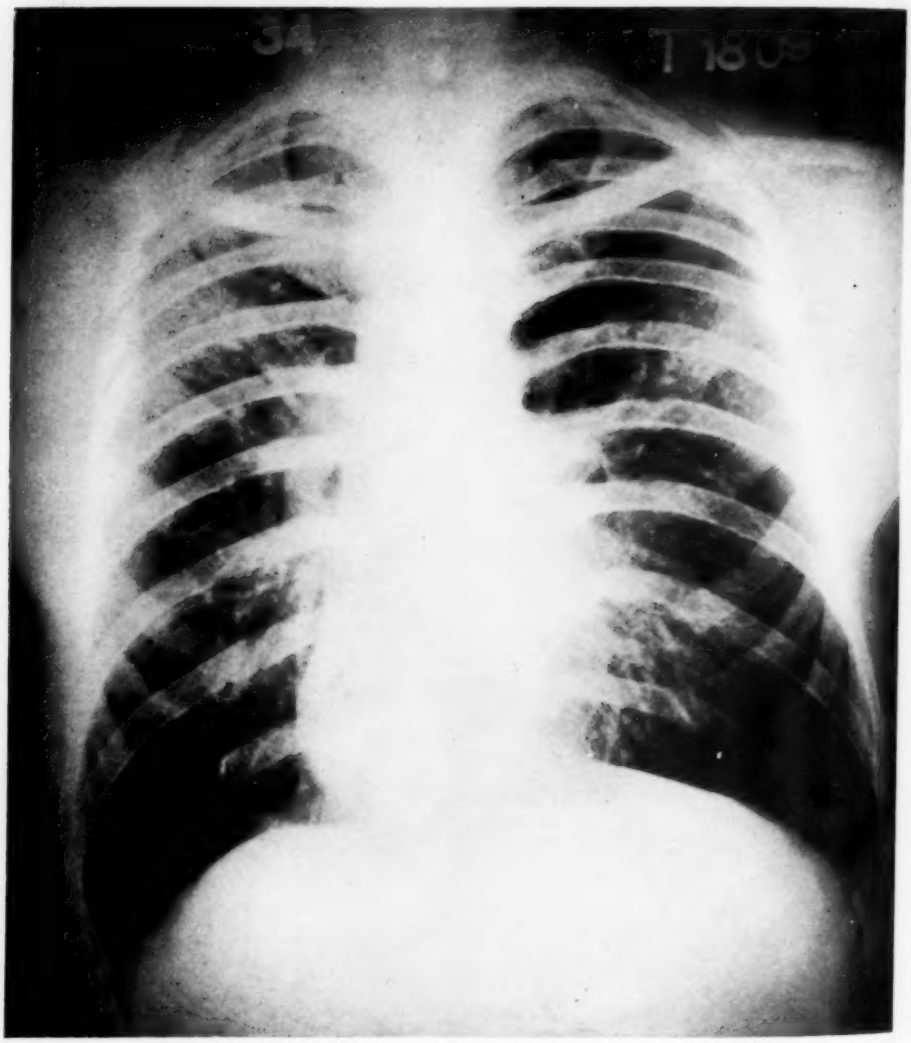

FIG. 3. Roentgenogram of chest, February 12, 1934.

Treatment. Methenamine tetraiodide (siomine) 0.65 gm., was given twice daily for two months, but discontinued because it had given rise to some digestive disturbance and had produced no appreciable effect on the roentgenographic appearance of the pulmonary lesions.

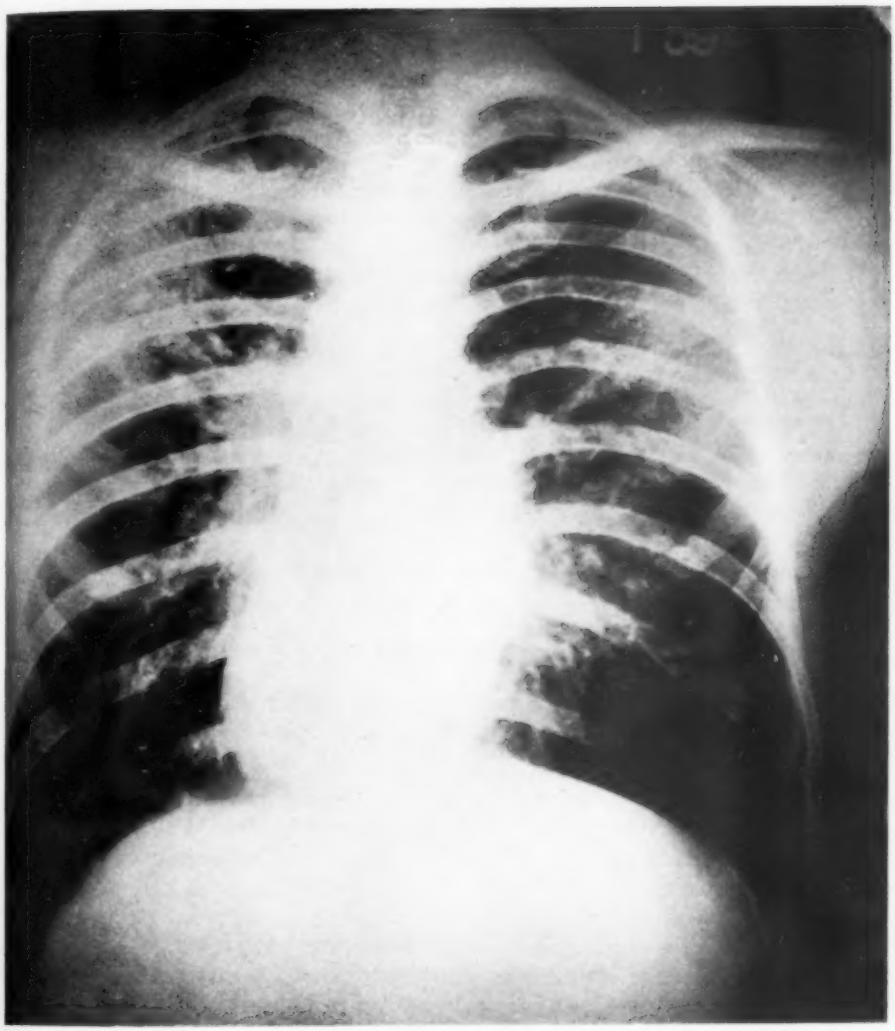

FIG. 4. Roentgenogram of chest, June 22, 1934.

DISCUSSION

The lesions shown in roentgenograms of the chest made in May 1930 were considered typical of pulmonary tuberculosis; however, all sputa in this case, examined at two other hospitals prior to admission to our institution, and over a period of one year while under our observation, were negative for acid fast bacilli. Animal inoculation was negative in April 1933. It is believed that this case tends to confirm the opinion expressed by Stoddard and Cutler [2] and Sheppe,[4] that torulosis of the lungs offers a better prognosis than other types of infection with this organism.

Acknowledgment is made to Major Rufus L. Holt, M. C., U. S. Army, and to Dr. Arthur T. Henrici, Professor of Bacteriology, University of Minnesota Medical School, for the laboratory studies necessary in isolating and identifying the organism. Final identification, on the basis of cultural characteristics and virulence tests, was made by Dr. Henrici.

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PRIMARY TUMORS OF THE HEART

With Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis before Death *

By SAMUEL A. SHELBURNE, *Dallas, Texas*

RARE is the opportunity to see a case of primary tumor of the heart, so the relatively little written on this subject is not surprising. Because of this rarity, the diagnosis is seldom considered before death. Gottel [1] (1919) has given Pavlowsky credit for making the clinical diagnosis of a primary tumor of the heart. The only other instances of heart tumor that have been suspected before autopsy were in patients with known primary tumors elsewhere in the body, who developed unexpected signs of heart disease, such as heart block, or cardiac decompensation (Fishberg,[3] Willius and Amberg,[5] Rosler [4]). Yater [2] has written a splendid review of this subject, to which the reader is referred.

I wish to present here a syndrome which was encountered in a young negro and led to a logical diagnosis of a tumor of the heart when there was no clinical sign of a primary tumor elsewhere in the body. He developed a rapid accumulation of fluid in the pericardial sac, which, on aspiration, proved to be serosanguinous. This was accompanied by the development of the *signs* of acute cardiac decompensation. The fluid reaccumulated very rapidly despite the removal of large quantities at frequent intervals. There was no fever, no history of fever, cough, night sweats, and no weight loss to suggest tuberculosis; furthermore, roentgenograms of the chest eliminated the possibility of pulmonary tuberculosis and a spinal puncture showed no evidence of tuberculous meningitis. Rheumatic pericarditis was made very unlikely both by the

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sanguinous nature of the fluid and the absence of fever. Pneumococcus, streptococcus, or other bacterial infections, could be eliminated as possible causes for the same reasons, and the culture of the fluid was negative. Lues (gumma) would be a remote possibility and it was made even more remote by the negative results of the blood Wassermann and Kahn tests. Furthermore, the spinal fluid Wassermann and colloidal gold tests were negative. The fluid did not clot on withdrawal and the red cell count was not high enough to suggest the rupture of a blood vessel or an aneurysm leaking into the pericardium. After the diagnosis had been recorded, an electrocardiogram showed partial bundle branch block, which has been recognized as a common finding in cardiac tumor (Willius and Amberg,[5] Rosler [4]). Therefore, we felt fairly confident of the correctness of the diagnosis and presented this case to the fourth year class as a tumor of the heart.*

We believe that, if this possibility be borne in mind when a bloody pericardial effusion is encountered, it will not be illogical to hazard this diagnosis. Two other cases of primary tumor of the heart were found in a review of 1200 autopsies and both of them had almost the same symptoms. These two cases, with complete postmortem examinations, are included in this report. It is worth while to bear in mind that, if this diagnosis can be made early, it may be possible to influence the patient's course with irradiation, as many of these tumors are of a type usually considered radio-sensitive.

Clinical Record

Case 1. S. R. was a married negro laborer, 24 years of age, who walked into the Parkland Hospital on December 12, 1933, complaining of generalized abdominal pain and distention, a hacking cough and fainting spells for a period of only five days. He stated that he was in good health, had done strenuous labor until the onset of the above symptoms, and had noticed no fever, sweats, or chills, and no hemoptysis. Since the onset he had developed persistent generalized colicky pains in the abdomen and an increasing feeling of distention, which was only partially relieved by bowel movements. This pain was not relieved by soda and had no relation to meals, or to the type of food. He had fainted, without warning, two or three times during this period. He thought he had been a little short of breath but was not sure. There had been no swelling of the legs.

He had had an easily cured penile lesion eight years previously. The past history was otherwise negative. The family history was irrelevant to his present condition.

On his admission examination, he was described as a well nourished and developed young negro, not acutely ill. The systolic blood pressure was 120, the diastolic 90; pulse 80; respirations 20. The temperature was 97.3° F. and varied from 97° to 98° until a few hours before death. The skin was normal. There were no enlarged lymph nodes. The pupils reacted to light and accommodation. The heart was moderately enlarged, the sounds distant, but there were no murmurs. The lungs were normal; no râles were heard at apices or bases. The liver was enlarged and tender, and there was moderate abdominal distention. The rectal examination and the genitalia were negative.

* It is interesting to contrast the method of diagnosis in this case with the keen reasoning and erudition shown by Pavlowsky in his case of a primary tumor of the heart. He noticed that his patient had the signs and symptoms of mitral stenosis when sitting or standing, but not when lying down. This suggested a tumor in the left auricle, which fell into the mitral orifice when the heart was vertical. The tumor was present but was in the right auricle.

The blood Wassermann and Kahn tests were negative. A spinal puncture was done and the pressure was 30 mm. Hg, but the fluid was normal to all tests, including Wassermann and colloidal gold. The hemoglobin was 80 per cent; red blood cells 3,970,000; white blood cells 8,000, with normal differential count. The urine specific gravity was 1032; it contained no sugar, but did contain one plus albumin. A moderate number of hyaline casts and about 50 pus cells per low power field were found. The blood sugar measured 105 mg., urea nitrogen 32 mg., and creatinine 1.5 mg. per 100 c.c. Two sputum examinations revealed no tubercle bacilli, and few pus cells.

The diagnosis at this time was uncertain. On December 16, the patient began to cough up blood-stained sputum, but there was no fever. He was very uncomfortable with some dyspnea and had to have morphine for relief. The next morning he was found with the signs of fully developed cardiac decompensation, with extensive pitting edema and dyspnea, but he never became orthopneic. There was great enlargement of the area of cardiac dullness and the heart sounds were distant. The diagnosis of pericardial effusion was suggested and a roentgenogram of the chest confirmed this. The acute decompensation was thought to be due to the rapid accumulation of fluid in the pericardial sac.

In the early evening, I was asked to see the patient and the following notes were made on the clinical record: "This morning, he awoke with extensive edema. There is marked increase in the venous pressure. There is an enormous increase in the precordial dullness and it rises high on the left upper border. There is no Broadbent sign. The condition is suggestive of pericardial effusion, as first postulated by Dr. Swift." Dr. Swift then withdrew about 900 c.c. of bloody fluid which did not clot. The dullness decreased on the upper border but not on the left border. The patient experienced little relief.

The next morning the writer made the following note: "The eye grounds are negative. The patient is still very ill. Precordial dullness is still very wide; the sounds distant. Dullness is now present at the left base with egophony and râles (either pneumonia or compression of lung from pericardial effusion). The best possibilities here seem to be: (1) tumor of the heart and pericardium, primary or secondary; (2) tuberculosis of the pericardium; (3) acute pericarditis, associated with pneumococcus septicemia, or a local infection (as rheumatic); (4) gumma of the pericardium. When other signs are considered (no fever, etc.), I believe this is a pericardial and cardiac tumor, either primary or secondary." There was no evidence made out clinically of a primary tumor elsewhere.

An electrocardiogram (December 18) showed a rate of 95, regular rhythm, P-waves normal, P–R interval 0.16 second, QRS slurred and slightly notched in all leads, main deflections downward in Lead I and upward in Leads II and III. QRS intervals, 0.16 in Lead I, 0.12 in Lead II, 0.16 in Lead III. The T-waves were diphasic in Lead I and Lead II and flat in Lead III. The picture was typical of that of partial bundle branch block. Complete block and bundle branch block have been used in the past as evidence of tumor of the heart in cases with known malignant growths elsewhere (Rosler, Willius and Amberg).

We were unable to relieve the patient's distress by repeated pericardial aspiration. The fluid always presented the same bloody appearance. Laboratory study showed it to contain 1,250,000 red blood cells; 1,400 white blood cells; lymphocytes 91 per cent, polymorphonuclear leukocytes, 9 per cent. Culture yielded no growth.

These subsequent developments confirmed our belief that the most logical diagnosis was tumor of the heart. At a clinic for fourth year students we based this on the following considerations: (1) the rapid reaccumulation of a bloody fluid suggested tumor; (2) tuberculosis was unlikely, as there was no clinical or roentgenographic evidence of pulmonary phthisis; (3) acute infections as pneumonia, streptococcic septicemia, or rheumatic fever, were ruled out by the nature of the cells in

the fluid, lack of fever and leukocytosis; (4) lues was unlikely because of the negative blood and spinal fluid Wassermann tests; (5) rupture of a vessel into the pericardium was ruled out by the comparatively low red cell count and the fact that the fluid did not clot.

The patient was desperately ill at this time, and it was hoped that drainage, more adequate than aspiration, would relieve him so that subsequently irradiation therapy could be tried. A pericardiotomy was therefore performed by Prof. Weaver on December 19 and exposed a massive invading tumor confined to the left auricle and upper half of the left ventricle. Drains were left in place and the wound closed.

The patient died about eight hours after the operation, and permission was granted for only a partial autopsy. The tumor seemed to be confined to the heart. It involved a large part of the left auricle, invaded the auriculo-ventricular septum, and extended into the left ventricle about half way to the apex. It was not in any sense circumscribed but seemed to be growing in every direction. The tumor was a pale, reddish gray color. A large mass 5 by 5 cm. was removed for microscopic study but we were unable to obtain the entire heart. The liver could not be palpated soon after death. Doubtless the enlargement before operation was due to passive congestion.

Microscopic Examination. The specimen submitted for microscopic study consisted of one main mass measuring 3.5 by 1.5 by 1.2 cm.; a second mass about two-thirds as large, and several other smaller fragments. Sections prepared from the two main masses of tumor tissue presented strikingly different structures.

One representative area of tumor (figures 1 and 2) is formed of loosely spaced cells with rounded nuclei and varying amounts of cytoplasm. The nuclei possess moderate amounts of chromatin and appear slightly vesicular. A single prominent nucleolus is present in many of the nuclei. The outer border of the cytoplasm of the tumor cells is often irregular and sometimes indefinite, and delicate processes seem to arise from many of the cells. No definite grouping of the tumor cells is evident except in regions where degenerative changes are marked. In these regions, the tumor cells are closely packed about the unobstructed blood vessels of the area, with slightly longer axes vertical to the walls of the vessels. Mitotic figures are only moderately numerous and the variations in chromatin content of the nuclei of the tumor cells are not marked. The nuclei are of fairly uniform size, and only an occasional larger and more hyperchromatic nucleus is seen. This area of tumor is imperfectly and coarsely lobulated by bands of mature fibrous tissue composed of coarse collagen fibers. In some regions these fibrous bands are edematous and a few recent hemorrhages are seen in focal areas, while other areas contain a brownish blood pigment having the appearance of hemosiderin. More delicate fibrous strands with moderately large and well developed blood vessels extend into the masses of tumor cells constituting the lobules of the tumor. In some regions much of the tumor is necrotic and the blood vessels of these areas frequently contain fibrin thrombi.

Sections from a different portion of the tumor (figures 3 and 4) reveal a spindle cell structure in striking contrast to the portion of the tumor above described. The tumor in this portion is more compact, and appears distinctly fibrous. The tumor cells are arranged in bands which have a tendency to form indefinite whorls. The nuclei are mostly oval or spindle shaped; their moderate chromatin content is distributed in granular form. Nucleoli are present, but are slightly less conspicuous. The cytoplasmic masses are elongated and apparently possess processes. In some areas, the cytoplasm appears vacuolated, the nucleus being surrounded by scattered protein granules. Where vacuolization is most marked, the tumor tissue has a reticulated appearance, and the fibrous structure is less prominent. A few recent hemorrhages and hemosiderin pigment are present in widely scattered focal areas. The intercellular substance is formed of delicate fibrils together with a granular

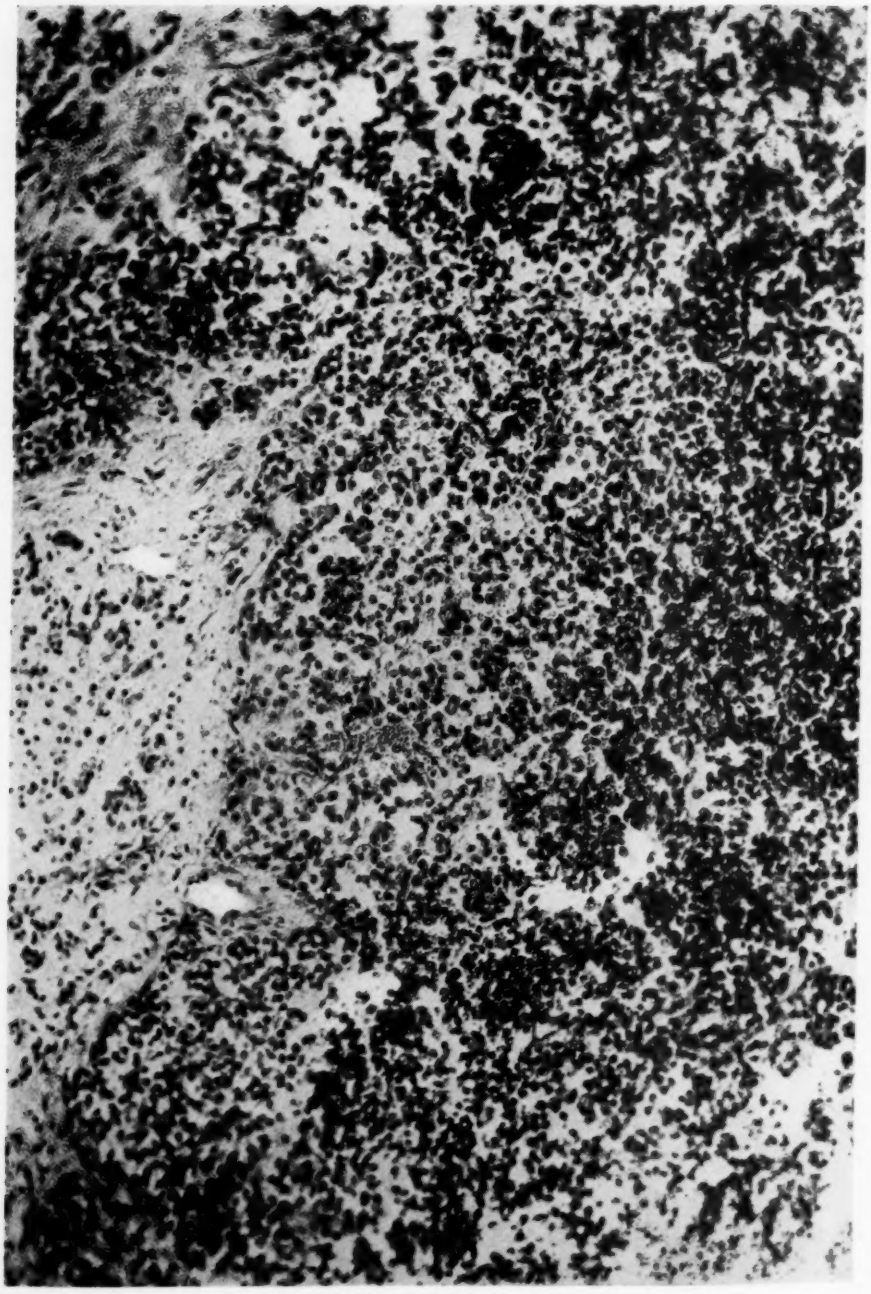

FIG. 1. Heart tumor. Low power magnification shows undifferentiated cells of irregular rounded type.

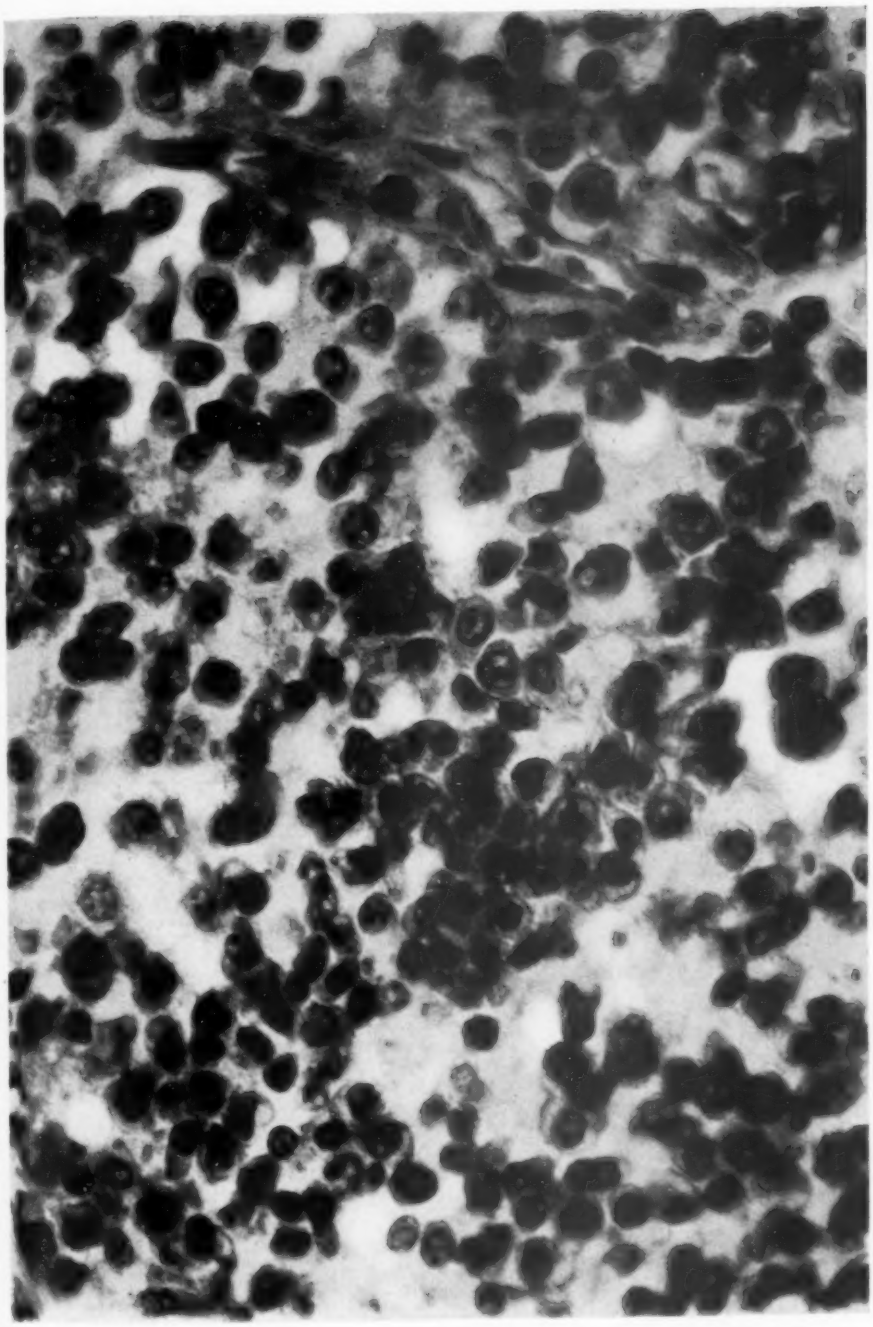

FIG. 2. Heart tumor. Higher magnification shows cell detail of undifferentiated round cell area.

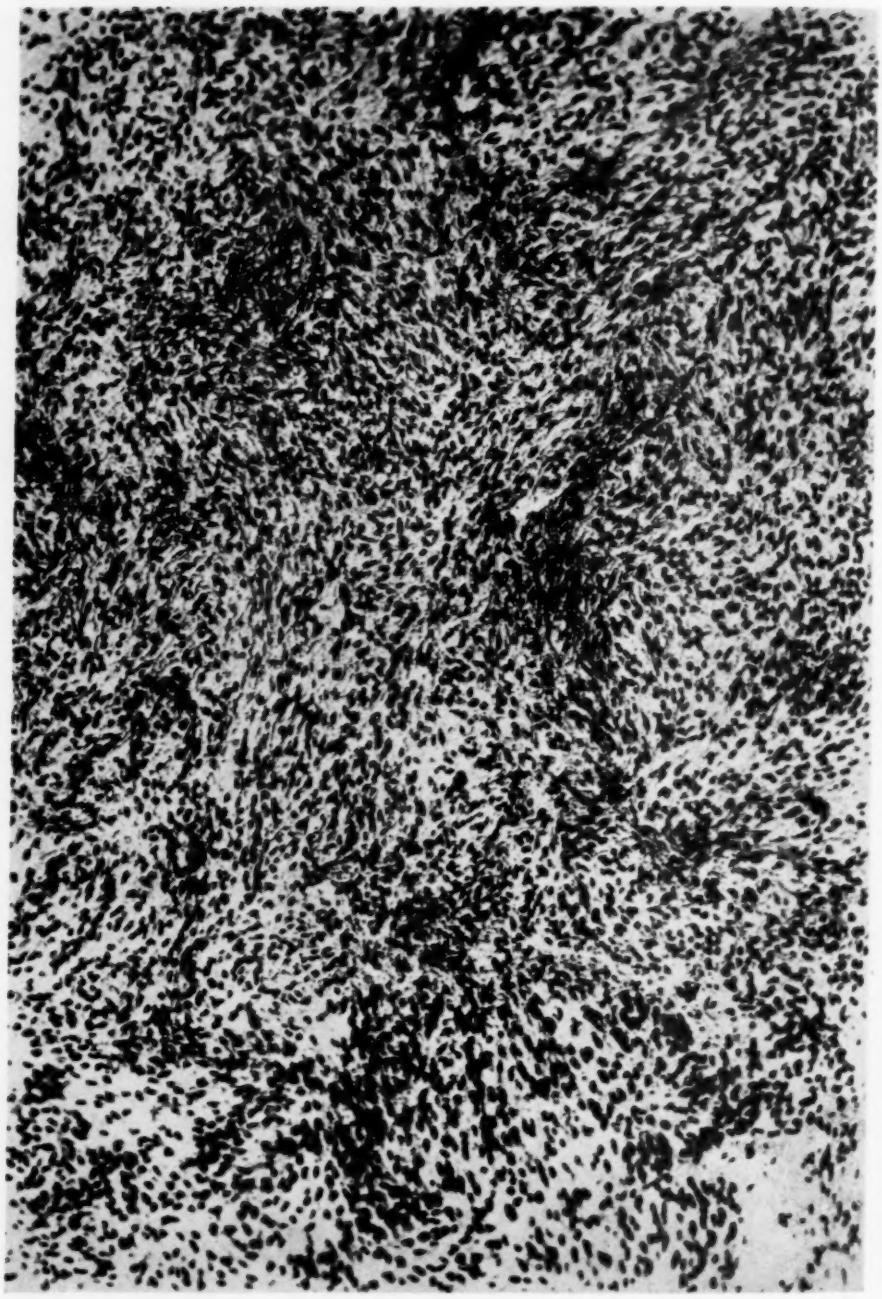

FIG. 3. Heart tumor. Low power magnification shows more differentiated area composed of spindle-shaped cells.

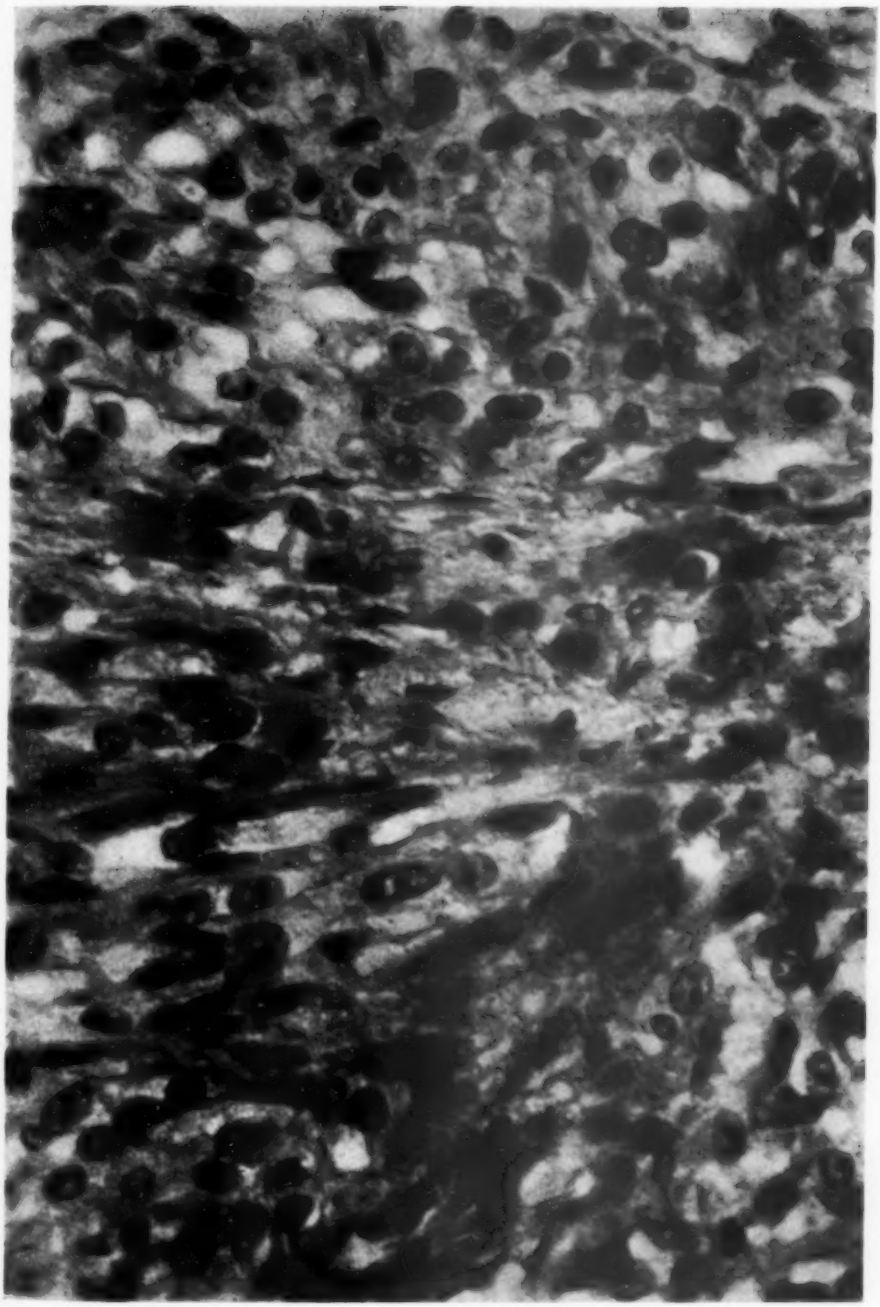

FIG. 4. Higher magnification shows cell detail of more differentiated area composed of spindle-shaped cells.

precipitate similar to that of edematous tissues. Mitoses are infrequent and nuclear variations are not marked.

The appearance is that of a moderately well-differentiated, invasive tumor of sarcoma type. Although the histogenesis of this tumor has not been determined, its structure suggests a peripheral nerve origin.

Prof. George T. Caldwell found two other cases of primary tumor of the heart in the records of the Department of Pathology of the Baylor University with careful and complete autopsy reports on each. He has added our case (case 1) to these as a part of his exhaustive study of the pathological findings which he will report later. It is important to note that the microscopic features on the tumor in case 1 are almost identical with those of case 2. The origin of the tumor in the latter was proved by a complete autopsy to be in the heart.

The clinical features of the earlier cases were very similar to those of case 1, but in neither of these was the pericardial effusion suspected. Both patients were young individuals with an acute onset of decompensation, with no previous history of heart disease. or any discoverable cause for heart disease. There was no fever and no evidence of tuberculosis and both had negative Wassermann tests.

Case 2. B. J. H., a white woman 22 years old, was admitted to the Baylor Hospital on September 6, 1932, complaining of a persistent hacking cough and epigastric pain for eight days. She had had nausea and vomiting during an otherwise normal pregnancy, which had terminated seven weeks before. The nausea and vomiting increased with the onset of the above symptoms.

On examination she was described as a young, fairly well developed white woman lying in bed and vomiting small amounts of yellow fluid. The temperature varied from 97° to 98° F. during the four days in the hospital and the pulse fluctuated from 100 to 116, the respirations from 18 to 22. There was edema of the eyelids, face and legs; also evidence of free fluid in the abdomen. The edema increased rapidly during the next three days. There was slight cyanosis. The apex beat of the heart was thought to be within the mid-clavicular line. The heart sounds were of good quality; blood pressure, systolic 110, diastolic 80. The liver was felt 12 cm. below the costal margin. The symptoms increased, but no new physical findings were made out. She died on the fourth day after admission.

Laboratory studies: The Wassermann test was negative; the hemoglobin 65 per cent; red blood cells 3,560,000, white blood cells 12,000 to 18,000, with 80 per cent polymorphonuclear leukocytes. The urine showed a small amount of albumin, many hyaline and granular casts, and a few red blood cells. The blood urea was 85 mg. and blood sugar 115 mg. per 100 c.c.

The autopsy revealed about 1000 c.c. of bloody fluid in the pericardial sac. There was a large, firm, yellowish tumor mass in the left ventricle, posteriorly and anteriorly along the septum and several smaller masses about the base of the heart attached to the great vessels. There were secondary tumors in the lungs and pleura. and a metastatic mass in the right suprarenal gland. The liver was not found enlarged. Doubtless the antemortem enlargement was due to extreme congestion. Microscopic examination of the tumor showed a primary sarcoma of the heart, very similar in appearance to the tumor in case 1.

Case 3. F. C., a 38 year old Mexican, was admitted to the Parkland Hospital in January 1926, complaining of cough of two weeks' duration, dyspnea, swelling of the abdomen and legs for the past three weeks. He also stated that he had had pain in the left shoulder, back and left side of the chest of increasing severity for three years.

Dyspnea and general anasarca were noted on examination. The pulse rate was 60 and irregular, respirations 20. There was no fever. The heart sounds were weak and distant, and the precordial dullness extended past the mid-axillary line into the sixth interspace. The apex beat was neither seen nor felt, and no murmurs were heard. The lungs were clear on percussion and auscultation. The abdomen was distended with fluid, and the liver and spleen were not palpable.

Laboratory examinations: The Wassermann test was negative; the hemoglobin was 80 per cent; the red blood cells numbered 4,840,000, white blood cells 9,650, polymorphonuclear leukocytes 70 per cent. The blood urea and sugar were normal. The sputum contained no acid-fast bacilli. A chest roentgenogram showed an enlargement of the heart shadow. The lung fields were clear.

At autopsy a large pericardial sac contained 1500 c.c. of bloody fluid which was not clotted. The heart was not enlarged, but the surface, especially over the left auricle and ventricle, was roughened by thick nodular areas which were seen and felt beneath the epicardium. The endocardium and valves were normal. There were no metastatic lesions except in a peribronchial lymph node, and this was only about 0.2 cm. in diameter. Ascites, a serous effusion in the right pleural cavity, generalized edema and passive congestion of the viscera were noted. The liver was not enlarged.

The microscopic sections proved the tumor to be a mesothelioma of the pericardium.

Summary

This report, the second in medical literature, describes the signs, symptoms and histologic appearance of a primary tumor of the heart which was correctly diagnosed before death. According to Gottel (1919), the first clinical diagnosis of this condition was made by Pavlowsky. The differential diagnosis which led to the correct assumption in this instance was also found applicable in two others found among autopsy records; it should lead more frequently to the correct diagnosis, whenever an otherwise unexplainable bloody pericardial effusion is encountered. Other signs and symptoms have not infrequently led to a diagnosis of secondary tumor; but are unreliable in the diagnosis of primary tumors.

I wish to thank Prof. George T. Caldwell for his aid and encouragement.

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EDITORIAL

THROMBOPENIC PURPURA

To Kaznelson's original suggestion of nineteen years ago, that splenectomy is a curative measure in thrombopenic purpura, little more has been added. The disorder, as earlier, retains its main divisions, as occurring in a primary or idiopathic form, and in a symptomatic variety secondary to other disorders. Although we are essentially concerned with the primary form, the existence of the secondary form is of the utmost diagnostic importance for the reason that in this secondary form splenectomy is not only contraindicated but may be actually harmful. The conditions most frequently giving rise to symptomatic purpura are sepsis, infectious diseases, drug poisoning, atypical acute leukemia, and aplastic anemia, the last being the most important.

At the time of Allen Whipple's review of cases in 1926, about 100 operations had been performed and the early results had amply confirmed Kaznelson's contention. Whipple's cases were divided into two groups representative of both the acute and the chronic variety, the former including so-called purpura fulminans, a rapidly fatal form uncontrolled by any known means. The operative mortality was about as one would expect with this type of risk, 8 per cent in the chronic cases and 90 per cent in the acute. This was the first crystallization of opinion based on a large collected series of cases and, while most useful, could necessarily give only limited information regarding the late stabilized effects of splenectomy on the natural history of the disease. We have as yet no knowledge based on well considered accumulated experience that answers the question, when, exactly, should splenectomy be performed. When should the clinician, on whose shoulders rests the responsibility, definitely recommend that the spleen be removed?

As inferred, the indications for operation are not so clearly outlined as to make the clinician's task an easy one. It will be agreed that as an emergency measure for acute purpura, when excessive bleeding cannot be controlled by any other means now known—rest, transfusion or irradiation—splenectomy should be performed, provided always that the form of purpura present is definitely primary. Palliative measures being of no avail, it remains for the surgeon to perform as safeguarded an operation as possible, accepting a high mortality in the hope of saving an occasional patient among a group otherwise doomed.

Chronic purpura, or purpura of less severity, offers opportunity for greater differences of opinion. A common problem of this type is the case seen during a prolonged mild attack or in one of a series of recurrences. The degree of platelet reduction may be only moderately severe and quite usually all of the other signs and symptoms are relatively mild. Yet since the diagnosis is primary thrombopenic purpura such a case faces potential

dangers. The clinician confronted by such a situation today will search vainly for sufficient data to enable him to answer confidently the questions which inevitably arise: Will the patient outgrow this disorder? Does spontaneous cure ever occur? Is the tendency of this particular patient toward recovery, toward greater severity, or if toward immediate recovery, toward increasingly severe attacks? If the patient under observation gives some indication of immediate recovery, should splenectomy be recommended at once, should it be deferred until recovery is apparently complete and then performed—an "interval splenectomy"; or should it be deferred until another more acute and less controllable attack occurs? These questions are answered differently by different men, and the lack of agreement no doubt must be due to insufficient or contradictory experiences.

How useful it might prove if there existed a "Purpura Registry" comparable to the Bone Tumor Registry of the American College of Surgeons. The function of such a registry could be the collection and study of the early and late histories of all cases of purpura. Most useful, too, would be the study of cases in which splenectomy had not been performed. Such a collection might reveal much now unknown concerning the natural history of the disease. Many would like to know more of the connection between the appearance, or the exacerbation of symptoms in apparently true idiopathic purpura, and upper respiratory infections or tonsillitis. What effect does tonsillectomy have in these cases? Have any of these patients, in whom splenectomy for one reason or another has been avoided, subsequently died in an acute attack?

Study of the therapeutic management of these cases in groups sufficiently large for comparison would decide between well known differences of opinion. For example, regarding transfusion, there is no unanimity as to whether or not the direct method offers advantages over the indirect. The amounts, frequency, and timing of transfusions with regard to operation are other uncertain features.

In the group operated upon, what percentage has subsequent bleeding? How severe or fatal are these recurrences? A registry of these cases might result in more complete late studies, with regular or seasonal observations. It might conceivably uncover certain features common to groups of cases whose subsequent courses have been similar.

A surgeon who has had the experience of operating on fairly acute cases of thrombopenic purpura, who has found it necessary literally to line his incision with hemostats, and then after removal of the spleen, even while closing the abdomen, has been amazed at the dryness of the wound, is apt to be more convinced of the specificity of the operation than is his medical colleague who may, during the succeeding months, observe one or more relapses of symptoms usually, however, much less severe than before the operation. A study of such operative and postoperative results would furnish a basis for convictions regarding treatment of the so-called chronic or only moderately severe cases.

The opinion of some today is that since we have insufficient basis for prediction as to the future serious dangers confronting the individual mild case of chronic thrombopenic purpura there is less risk in an immediate splenectomy than in expectant treatment. The risk of a properly conducted operation even in moderately severe cases may well be less than that of a deferred operation in the same case undertaken finally as a last resort.

Whether this or some quite different policy will eventually prove to be best founded can be determined only through further study and especially through systematic pooling of experience with treatment of the disease.

EDWARD M. HANRAHAN

REVIEWS

Clinical Management of Syphilis. By ALVIN RUSSELL HARNES, M.D. 71 pages; 14.5 × 22 cm. Macmillan Co., New York. 1935. Price, $1.50.

The author discusses the problem of the therapy of syphilis and furnishes practical schedules of treatment according to the stage of the disease. The importance of system and a definite plan is stressed. Complicating factors such as cardiovascular involvement are dealt with rather briefly. In discussing post-arsphenamine reaction the warning value of itching and of slight icterus should have been emphasized. Dr. Harnes is almost alone among syphilologists in recommending sulpharsphenamine. In spite of the drawbacks necessarily present in such a brief discussion of an important subject, this small book will have a definite value for the general practitioner.

H. M. R.

Food and Health. By HENRY C. SHERMAN. 296 pages; 14 × 20.5 cm. The Macmillan Co., New York. 1934. Price, $2.50.

This book is written in simple, non-technical language. Its chief purpose is "to guide the reader to well-balanced judgments in the daily choice and use of food." The solid and noteworthy contributions of the author to the science of nutrition, as well as his widely used treatises on the Chemistry of Food and Nutrition and on Food Products, which are well recognized standard works of reference, make anything he says worthy of respect and attention. It must, however, be confessed that there is little that is very new in this work or that has not been quite as well and attractively presented elsewhere. The author is emphatic in driving home the thesis that at least half of the food calories of the diet should be in the form of the "protective foods" and that at least half of whatever cereal products are consumed should be of the whole grain variety. The last third of the book is devoted to tables of the caloric values of the customary servings of foods; of their content in proteins and minerals; of vitamin values; and of illustrative records of actual meal menus—one prolonged over a period of six months. There is an interesting bibliography of publications on diet and nutrition, largely recent, and a good index. One is always impressed with the debt which every author of books on food and nutrition owes to the publications of the United States Department of Agriculture, an obligation which Dr. Sherman candidly acknowledges on page 208.

G. A. H.

The Nervous Patient. By CHARLES PHILLIPS EMERSON, M.D. 463 pages; 14 × 21 cm. J. B. Lippincott Co., Philadelphia. 1935. Price, $4.00.

This volume is an attempt to supply a clearer understanding of the emotional components of the patients who come into a general practitioner's office. The first five chapters (of thirty) present the author's views of the allergic and autonomic endocrine mechanisms by which physical symptoms are produced. The next thirteen chapters go through the body by symptoms, ostensibly to point out the nervous concomitants of various disease pictures.

This is all done in 176 pages filled with various symptoms which "may occur" or are "not infrequently seen." It reminds one of the paragraphs in many texts in which the more unusual variations of common chemical syndromes are mentioned, and is not a satisfying presentation. The psychological aspect of treatment is rarely more than referred to.

The remaining twelve chapters take up sleep disorders, disturbances in the sex life, the psychoneuroses and the psychoses. It is a superficial study. The psychopathology is a mixture of various schools of thought. We doubt if many psychiatrists would agree with any of the formulations. Treatment is by rest, diet, nightly reading of the Psalms and exhortations to make "social efforts with high spiritual aims." Bromides are prescribed in large doses. Psychoanalysis and intensive psychotherapy are dismissed with a mention. The newer concepts are not mentioned.

In spite of all this, it is not a bad book. After all, when a "nervous patient" comes into the office the physician wants to know what to do about it. In this book he will find treatment outlined in some detail. Psychiatrists would sniff at it but no doubt a great many patients may be relieved of their most troublesome symptoms by the means Dr. Emerson suggests.

H. M. M.

Public Health Nursing in Industry. By VIOLET H. HODGSON, R.N., Assistant Director of the National Organization for Public Health Nursing; foreword by C.-E. A. Winslow, Dr. P.H., Yale University. xxii + 249 pages; 14 × 20 cm. Macmillan Company, New York. 1933. Price, $1.75.

The purpose of this book, "to indicate the potential field of public health nursing in commerce, trade and industry," is well brought out both from the viewpoint of the nurse engaging in this type of work and of the organizations needing this service. It opens up to the nurse a vast undeveloped field needing leaders and workers for building up health programs for employees as well as the curative and rehabilitative work to which we have become accustomed. For the executives there are many points pertaining to the position of the nurse in industry, many suggested possibilities for development in the various organizations resulting in better health of employees and thereby increased output of production.

The book is divided into two parts, Part I dealing with Company Organization and Administration, Part II with Nursing Service, The Principles, Practices and Procedures. The material is well arranged for easy reference and written in a simple but stimulating style. Many ideas and suggestions are given for planning, organizing and equipping such a department, as well as for complete and accurate record-keeping.

The personality and qualifications of the industrial nurse are also included. The need for a deep interest in people and for "the ability to make her services freely accessible," however, does not seem any reason for a departure from a professional bearing. While this type of nursing is a specialty and requires postgraduate courses for filling many of the higher positions, it is possible, though in all too few schools, to receive a course in Public Health Nursing in the basic undergraduate course which will fit one for many positions in this field.

Roots of Crime: Psychoanalytic Studies. By FRANZ ALEXANDER, M.D., Director, Chicago Institute for Psychoanalysis, and WILLIAM HEALY, M.D., Director, Judge Baker Guidance Center, Boston. 305 pages. Alfred A. Knopf, New York. 1935. Price, $3.00.

This book presents the case histories of 11 criminals, 10 men and one woman, who were studied and treated by the psychoanalytic technic as applied by Dr. Alexander. Seven of the cases were reported as successful analyses, and four as unsuccessful attempts. This project was a piece of research undertaken to determine, if possible, the traits that are likely to produce delinquency and at what age they begin. The study was financed by a grant from the Julius Rosenwald Fund.

This new approach to the study of the criminal is painstaking and time-consuming, and as such it is recognized that it can be applied to only a few cases. Nevertheless, the authors in attempting to explore the causations of certain types of criminal careers, pursued a path that science, particularly in medicine, recognizes as offering the greatest promise of showing new ways to therapeutic achievement. The psychoanalytic method is extremely expensive, but if it could be applied to selected cases the expense would be nothing as compared with the social costs of long continued careers of criminality.

This study brings out the fact that some individuals, given chances for a normally pleasurable life after making a start in the paths of delinquency, find themselves unable to cease their delinquent trends under the very environmental circumstances which they themselves in full consciousness declare to be most desirable. These case histories demonstrate that any ordinarily or even extraordinarily good environmental changes may not bring about the desired checking of antisocial impulses when from early years unconscious motivations or drives have existed. Emotional factors of all kinds have been found active in creating inner tensions which the individual attempts to relieve by criminal acts.

Dr. William Healy has for many years been working in the field of criminology and was the first physician systematically to use the psychiatric approach in the study of the delinquent and criminal. He has contributed many books on the subject to medical literature and his name connected with this book unreservedly recommends it for serious perusal.

J. L. McC.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Dr. E. Cowles Andrus (Fellow), Baltimore, Md.—1 book, "Physical and Clinical Diagnosis";
Dr. Lee D. Cady (Fellow), St. Louis, Mo.—1 reprint;
Dr. John L. Goforth (Fellow), Dallas, Tex.—1 reprint;
Dr. Noxon Toomey (Fellow), Palmyra, Mo.—3 reprints;
Dr. Frank L. Williman (Fellow), Washington, D. C.—1 reprint;
Dr. V. W. Bergstrom (Associate), Binghamton, N. Y.—3 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint.

Through the initiative of Dr. Ignacio Chávez (Fellow), Mexico City, the "Mexican Society of Cardiac Studies" was founded and organized on May 27. The official headquarters of the Society is Artes 5, Mexico, D.F. The studies of the Society will be published in "Archivos Latino Americanos de Cardiologia y Hematologia." Dr. Ignacio Chávez was elected the first President and Dr. José Quintín Olascoaga was elected Secretary-Treasurer.

The following Fellows of the American College of Physicians will contribute to the Program of the Mississippi Valley Medical Society Meeting, known as the Tri-State (Illinois, Missouri and Iowa) Post-Graduate Assembly, at Quincy, Ill., October 2, 3 and 4:

Dr. William C. MacCarty, Professor of Pathology, University of Minnesota Graduate School of Medicine, Rochester, Minn.;
Dr. Albert Soiland, Chairman of the Malignancy Board, California Hospital, Los Angeles, Calif.;
Dr. E. Sanborn Smith, member of the Missouri State Board of Health, Kirksville, Mo.;
Dr. D. G. Stine, Professor of Medicine, University of Missouri School of Medicine, Columbia, Mo.;
Dr. G. M. Cline, Head of the Department of Pediatrics, Brokaw Hospital, Bloomington, Ill.;
Dr. F. G. Norbury, Associate Physician to the Norbury Sanatorium, Jacksonville, Ill.

Dr. Harold Swanberg (Fellow) Quincy, Ill., is Secretary-Treasurer of the Society.

Dr. William Devitt (Fellow), Physician in Charge and Superintendent of Devitt's Camp, Allenwood, Pa., was recently elected President of the Federation of American Sanitoria at the Federation Meeting in Albuquerque, N. M.

Dr. Simon R. Blatteis (Fellow) was recently appointed Chief of the Department of Medicine at the Jewish Hospital at Brooklyn.

Dr. Frank H. Krusen (Associate) has been appointed Director of the Section on Physical Therapy at the Mayo Clinic, Rochester, Minn.

Dr. Louis H. Behrens (Fellow), St. Louis, Mo., presented a paper on "Hyperpituitarism, A Report of Two Interesting Clinical Cases" on the recent Pan-American Medical Congress cruise to South America. The one case was the now well known "Alton Giant," whom Dr. David Barr (Fellow) and he have reported and observed now over five years.

Dr. George J. Wright (Fellow), Pittsburgh, has been appointed Professor of Neurology at the University of Pittsburgh School of Medicine, to succeed the late Dr. Thomas M. T. McKennan.

Dr. Henry S. Plummer (Fellow), Rochester, Minn., was the recipient of the honorary degree of Doctor of Science by Northwestern University at its last annual commencement.

Dr. Albert C. Broders (Fellow), Rochester, Minn., has recently accepted the appointment of Professor of Surgical Pathology and Director of Cancer Research at the Medical College of Virginia, Richmond.

Dr. Hugh J. Morgan (Fellow) has been appointed Professor of Medicine at Vanderbilt University School of Medicine, Nashville, succeeding Dr. Charles Sidney Burwell, who has been elected Dean and Professor of Research Medicine at Harvard University Medical School.

Dr. Vincent J. Dardinski (Associate) has been advanced to Professor of Anatomy and Director of the Department at the Georgetown University School of Medicine, Washington, D. C.

Dr. John T. Farrell, Jr. (Fellow) has been made Assistant Professor of Roentgenology at the Jefferson Medical College of Philadelphia.

Former associates of the late Dr. Aldred S. Warthin (Master), the first Editor of the ANNALS OF INTERNAL MEDICINE, recently presented to the University of Michigan School of Medicine a bronze plaque as a memorial to Dr. Warthin. Dr. Warthin had been for many years Professor of Pathology and Director of the Pathological Laboratory.

Dr. Ernest R. Zemp (Fellow), Knoxville, has been made President of the Tennessee Valley Medical Association.

Dr. Howard T. Karsner (Fellow), Professor of Pathology at Western Reserve University, has been elected to membership in the French Association for the Study of Cancer.

Dr. Millard E. Winchester (Fellow), Brunswick, Ga., commissioner of health of Glynn County, was recently tendered a dinner by the Brunswick Board of Trade,

in recognition of his county's winning first prize in the southeastern division of a rural health contest sponsored by the U. S. Public Health Service and the Chamber of Commerce of the United States. This county was the first in the state of Georgia to have the services of a paid health officer.

The Washington Society of Pathologists tendered a farewell banquet to Major Virgil H. Cornell, Secretary-Treasurer of the Society and retiring Curator of the U. S. Army. Lt. Col. William Denton (Fellow) is the new Curator and has been elected Secretary of the Society.

Dr. Coursen B. Conklin (Fellow) has been reëlected Secretary of the Medical Society of the District of Columbia.

Admiral Cary T. Grayson (Associate), Chairman of the American Red Cross, was recently appointed Chairman of the League of Red Cross Societies.

Dr. Louis H. Fligman (Fellow), Helena, Mont., was installed as President of the Medical Association of Montana, at its last annual meeting during July.

Dr. Jonathan C. Meakins (Fellow), Montreal, Que., Ex-President of the American College of Physicians, has been made a Fellow of the Royal College of Physicians of London.

Sir Frederick Banting (Fellow), Professor of Medical Research at the University of Toronto, was the recipient of the gold medal of the Society of Apothecaries of London, June 4, "for valuable services rendered to the science of therapeutics." Dr. Banting was also made a Fellow of the Royal Society, and on June 20 delivered an address on the history of insulin at the British Postgraduate Medical School, Hammersmith.

Dr. James B. Collip (Fellow), Professor and Head of the Department of Biochemistry at McGill University, Montreal, recently received the honorary degree of Doctor of Laws from the University of Manitoba.